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Naturalistic Studies on the Effects of Shift Work-Related Circadian Disruption on Diurnal Rest-Activity Behavior and Cardiac-Autonomic Patterns in Morning and Evening Type Police and Rescue Workers

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Abstract

Sleep is an essential and strictly regulated process that is vital for health and well-being. Shift work forcefully disrupts the natural rest-activity behavior of the body, such that physical activity occurs during the biological night, whereas rest behaviors, such as sleep, occur during the biological day. Shift work may result in circadian misalignment, a condition in which neither active nor rest behaviors can be performed at an optimal capacity during their respective dedicated intrinsic circadian windows of opportunity. The intrinsic circadian system and sleep-wake behavior each independently influence autonomic nervous system functions and require synchronization to ensure optimal performance and health. An individual's tolerance to shift work may be modulated by their chronotype and can be attributed to intrinsic variability in circadian and homeostatic characteristics. Increased mortality and cardiometabolic risk factors are observed in individuals with a later chronotype (i.e., evening preference for daytime activities and later bed- and waketimes) compared to individuals with earlier chronotypes. First responders are at elevated risk for cardiometabolic disorders due to shift work and trauma and stressor-related disorders due to routine occupational exposure to danger and trauma. This at-risk population therefore warrants urgent study and is well-suited to investigate both stress and shift work effects under naturalistic conditions.

In the first manuscript of this thesis, we report results of a validation study comparing the Fitbit Charge 2^{TM} to polysomnography in a sample of first responder shift workers under naturalistic conditions. Results show unbiased estimates of non-rapid eye movement (NREM) sleep with N1 sleep onset criteria but overestimation of REM sleep latency, wake after sleep onset and underestimation of HR. In the next manuscript, we explored the potential of this Fitbit device to capture rest-activity behavior in the same cohort and report sinusoidal oscillation in all sleep variables investigated, indicating intrinsic circadian regulation and entrainment to the 24-hour light/dark cycle, despite sleep/wake cycles adapted to shift work schedules. This was modulated slightly by chronotype, such that evening types slept longer during the morning and daytime; familiar phase advances were observed for morning types in sleep duration. Finally, we report findings of cardiac autonomic outcomes in this cohort and show that intrinsic circadian rhythms of HR and HRV are entrained to solar light/dark cycles, associated with higher HR in evening types but no difference in HRvar. Rest-activity behavior is also more irregular in evening types. We conclude by suggesting that the rest-activity behavior in our cohort reveals circadian misalignment. This has implications for the health and well-being of the individuals surveyed. Further research in is warranted to elucidate the role of shift work and circadian misalignment in adverse health consequences under naturalistic conditions.

Zusammanfassung

Schlaf ist ein lebensnotwendiger und streng geregelter Prozess, der für Gesundheit und Wohlbefinden unerlässlich ist. Schichtarbeit stört das natürliche Ruheaktivitätsverhalten des Körpers so stark, so dass körperliche Aktivität während der biologischen Nacht stattfindet, während Ruheverhalten, wie z.B. Schlaf, während des biologischen Tages auftreten kann. Schichtarbeit kann zu einer zirkadianen Fehlausrichtung führen, einem Zustand, in dem weder das Aktivitäts- noch das Ruheverhalten während dem jeweiligen intrinsisch optimalem zirkadianen Zeitfenster ausgeführt werden können. Das intrinsische zirkadiane System und das Schlaf-Wach-Verhalten beeinflussen, jeweils unabhängig voneinander, die Funktionen des autonomen Nervensystems und erfordern eine Synchronisation, um optimale Leistung und Gesundheit zu gewährleisten. Die Toleranz eines Individuums gegenüber Schichtarbeit kann durch den Chronotyp leicht moduliert sein und kann auf eine intrinsische Variabilität der zirkadianen und homöostatischen Charakteristika zurückgeführt werden. Erhöhte Mortalität und kardiometabolische Risikofaktoren werden bei Personen mit einem späteren Chronotyp (d.h. Bevorzugung der Abendstunden für Tagesaktivitäten und spätere Schlaf- und Wachzeiten) im Vergleich zu Personen mit früheren Chronotypen beobachtet.

Im ersten Manuskript beschreiben wir die Ergebnisse einer Validierungsstudie, bei welcher Fitbit Charge 2™ mit Polysomnographie anhand einer Stichprobe von Ersthelfer-Schichtarbeitern unter naturalistischen Bedingungen verglichen wurde. Die Ergebnisse zeigen erwartungstreue Schätzungen des NREM-Schlafs (Nonrapid Eye Movement) mit N1-Schlafbeginnkriterien, eine Überschätzung der REM-Schlaf-Latenzzeit, des Aufwachens nach Schlafbeginn und eine Unterschätzung der Herzrate. Im nächsten Manuskript untersuchten wir das Potenzial dieses Fitbit-Geräts, das Ruheaktivitätsverhalten in derselben Kohorte zu erfassen. Wir beobachten sinusförmige Veränderungen in allen untersuchten Schlafvariablen, was auf eine intrinsische zirkadiane Regulation und die Beteiligung des 24-stündigen Hell-Dunkel-Zyklus hinweist und dies trotz des an die Schichtarbeitszeiten angepassten Schlaf-/Wachzyklus. Dies wurde durch den Chronotyp moduliert, so dass die Abendtypen morgens und tagsüber länger schliefen; wohingegen bei den Morgentypen die weitgehend bekannten Phasenfortschritte bei der Schlafdauer beobachtet wurden.

Im letzten Manuskript zeigen wir kardio-autonomen Resultate aus dieser Kohorte auf und beobachten, dass intrinsische zirkadiane Rhythmen der HR und HRV zu solaren Hell-Dunkel-Zyklen gekoppelt sind, die mit einer höheren HR bei Abendtypen assoziiert sind, aber keinen Unterschied in der HRvar aufweisen. Desweiteren ist das Ruheaktivitätsverhalten bei den Abendtypen unregelmäßiger. Wir schlussfolgern mit der Vermutung, dass das Ruheaktivitätsverhalten in unserer Kohorte ein zirkadianes Fehlausrichtung aufweist. Dies hat Auswirkungen auf die Gesundheit und das Wohlbefinden der befragten Personen. Zukünftige Forschungsarbeiten sind notwendig, um negative gesundheitliche Folgen von Schichtarbeit und zirkadianer Fehlausrichtung unter naturalistischen Bedingungen zu beleuchten.

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Abbreviations

AASM	American Academy of Sleep Medicine
AN	Adaptation night
ATP	Adenosine triphosphate
AV	Atrioventricular node
BH	Benjamini-Hochberg
BN	Baseline night
BP	Blood pressure
CAPS-5	Clinician-Administered PTSD Scale for DSM 5
CCF	Cross-correlation function
CPD	Composite phase deviation
CRPP	Clinical Research Priority Program
DBP	Diastolic blood pressure
DeepD	Duration in deep sleep
DSM 5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DTS	Diurnal Type Scale
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
FDA	United States Food and Drug Administration
FFT	Fast Fourier transformation
GAMM	General additive mixed model
GND	Ground
HF	High frequency
HR	Heart rate
HR10	10%-Trimmed HR average
HRV	Heart rate variability
HRvar	Variance of heart rate
$HRvar_{10}$	10%-Trimmed HR variance
IBI	Inter-beat interval
KSS	Karolinska Sleepiness Scale
LF	Low frequency
Lightd	Duration in light sleep

LMER	Linear mixed effects regression
LoA	Limits of agreement
LOC	Left ocular channel
MCTQ	Munich Chronotype Questionnaire
MEQ	Horne-Östberg Morningness-Eveningness Questionnaire
mMid	Mean sleep midpoint
mSD	Mean sleep duration
mSO	Mean sleep onset time
N1	NREM stage 1 sleep
N1on	First occurrence of stage N1 indicating sleep onset
N2	NREM stage 2 sleep
N2on	First occurrence of stage N2 indicating sleep onset
N3	NREM stage 3 sleep
NE	Norepinephrine
NREM	Non-Rapid eye movement
OSA	Obstructive sleep apnea
PAI-1	Plasminogen activator inhibitor
PANAS	Positive and Negative Affect States
PCL-5	PTSD Checklist for DSM 5
PET	Positron Emission Tomography
PLMS	Periodic limb movement sleep
pNN20	Percentage of normal to normal intervals differing by >20%
pNN50	Percentage of adjacent normal to normal intervals differing > 50 ms in 24 h
PNS	Parasympathetic nervous system
PPG	Photoplethysmography
PSG	Polysomnogram
PSQI	Pittsburgh Sleep Quality Index
PSS-10	Perceived Stress Scale
PTSD	Posttraumatic stress disorder
QAVSD60	60%-Quantile of the absolute value of the second derivative
REM	Rapid eye movement
REM%	Percentage of REM sleep in the first NREM-REM cycle
REMD	Duration in REM sleep
REML/RL	Latency to REM sleep
rMEQ	Horne-Östberg Morningness-Eveningness Questionnaire - A Reduced Scale

RMSSD	Root mean square of successive differences
ROC	Right ocular channel
RPP	Rate Pressure Product
RSA	Respiratory sinus arrhythmia
SA	Sinoatrial node
SBP	Systolic blood pressure
SCN	Suprachiasmatic nucleus
SDNN	Standard deviation of normal to normal intervals
SNS	Sympathetic nervous system
Soff	Sleep offset
Son	Sleep onset
SOREMS	Sleep onset REM sleep
STAI	State Trait Anxiety Inventory
SWA	Slow wave activity
SWD	Shift work disorder
SWS	Slow wave sleep
TST	Total sleep time
VLF	Very low frequency
WASO	Wake after sleep onset
ΔMid	CPD of sleep midpoint
ΔSD	CPD of sleep duration
ΔSO	CPD of sleep onset

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1 Introduction

1.1 Sleep

Sleep is an essential and strictly regulated process that has been identified in all species carefully studied (Bushey et al. 2009), yet remarkably its core function remains a mystery (Cirelli and Tononi 2008). Indeed, it may be the only major behavior still in search of a function (Bushey et al. 2011). An evolutionarily adaptive but unknown value has been ascribed to sleep (Tobler 2000), and one may reasonably speculate that sleep serves some universal and advantageous function across species, as it has been conserved across species, whereas it is unknown whether sleep emerged once or several times throughout evolution (Cirelli and Tononi 2008). Such a line of reasoning would be the most parsimonious. A constant and recurring daily sleep quota is maintained through a balance between sleep duration and intensity, of which the electroencephalogram (EEG) derived variable known as slow wave activity (SWA) is a clear and reliable marker, although motor activity, arousal threshold and cardiovascular variables, such as heart rate variability, also serve as markers of compensatory systems which are enhanced after sleep has been restricted or deprived (Tobler 2000). Sleep is, perhaps in contrast to widely held assumptions, not a unitary state, but is highly variegated, nuanced and transient, with no truly finite or dichotomous beginning or end. A simple behavioral definition of sleep might include features such as a state of consciousness that is altered from waking, one characterized behaviorally (but not necessarily) by closed eyes, regular daily recurrence and reversibility, diminished responsiveness to environmental stimuli, relative physical inactivity (inhibition of all voluntary muscles) and habitual sleeping locations and typical body posture (Horne 1988). Despite these seemingly unambiguous indications of behavioral quiescence, the brain is highly active and demonstrates rich patterns of neuronal excitation and inhibition in the EEG which characterize distinct stages of sleep (Horne 1988).

Conventionally, electrical activity generated by the brain is recorded during sleep by an apparatus called the EEG by means of non-invasive electrodes that are affixed to pre-measured scalp locations according to the 10-20 System (Jasper 1958). This system divides the scalp into distances 10 – 20% of total distances between two physical landmarks, e.g., nasion to inion distance (Jasper 1958). The EEG is an important and practical tool in human sleep research. Electrode sites are given alphanumeric labels which correspond to the region of the cortex whose electrical activity they record and to what side of the scalp they are affixed. All electrode sites to the left of the corpus callosum are given odd numbers, whereas those electrodes to the right are given even numbers. For example, C3 indicates an electrode placed at the left central cortex, whereas P4 would indicate right parietal cortex placement. All electrodes placed over the corpus callosum receive the suffix “z” added to their cortical designation to indicate their placement on the “zero” line, such as Fz, which indicates frontal cortical zero line placement (Jasper 1958). In addition to scalp electrode locations, mastoid (M1, M2,

also termed A1, A2) references are used to enhance the signal-to-noise ratio of a given electrode signal, such that the electrical potential of the contralateral mastoid (indifferent electrode) is subtracted from the potential recorded from the electrode site of interest (active electrode) and is conventionally annotated "C3-M1," in the example of M1 signal subtracted from the C3 electrode signal (Martin 1991). The logic is that since the mastoid electrodes are placed on a bony process behind the contralateral ear, that their signal should represent general noise in the EEG signal and not endogenous electrical brain activity at the cortical site of interest. Alternative sites for reference have been used, such as the ear lobes and the nose. In addition to the scalp electrode sites, it is conventional to record eye activity by means of the electrooculogram (EOG) at each eye and muscle activity by means of the electromyogram (EMG) at the chin. The signals generated by the EOG and EMG are critical for identifying rapid eye movement (REM) sleep. In limited research contexts (e.g., for screening purposes), but routinely in clinical contexts, instruments for recording variables related to respiration, such as thermistors or respiratory belts, and leg movement, such as leg electrode sites, are implemented, to assess breathing disorders (e.g., sleep apnea or hypopnea) or restless leg disorder, respectively (AASM 2007). The electrocardiogram (ECG) is applied routinely in both research and clinical settings and is described in chapter 1.2. When EEG is combined with EOG, EMG and ECG the term polysomnography is used.

The cellular activity that underlies electroencephalography is attributable principally to the electrical activity of pyramidal cells in the cerebral cortex. Interestingly, it is not the action potential, but the synaptic potential, that contributes most significantly to the surface potential recorded by electrodes, due in part to the slowness of the synaptic potential compared to the speed of action potentials. For this reason, the synaptic potential possesses summate qualities. Pyramidal cells contribute more than other neuronal cell types (e.g., interneurons, stellate cells or basket cells) or glial cells because of their parallel orientation to each other and the perpendicular orientation of their dendrites with respect to the cortical surface. Thus, their dendrite-generated synaptic potentials may be recorded with little attenuation because sources and sinks share a perpendicular orientation to the surface of the cortex. Other cells of the cortex have no coherent orientation relative to one another or to other pyramidal cells and their influence is largely negligible (Martin 1991).

Frequency potentials recorded from the normal human brain range from 1 – 30 Hz, with amplitudes ranging from 20 – 100 uV. Amplitude can be modulated (e.g., diminished) by cerebrospinal fluid, the meninges or the skull and scalp, among other artifacts, such as sweat. Dominant frequency bands observed are defined as follows (Martin 1991), alpha (8 – 13 Hz), beta (13 – 30 Hz), delta (0.5 – 4 Hz) and theta (4 – 7 Hz). These frequencies are associated with underlying processes and states, such as relaxed wakefulness, in which EEG alpha activity is characteristically

present (Martin 1991), particularly over the occipital cortex, or slow-wave sleep, which is defined by the presence of delta activity, most strongly evident in frontal cortex (AASM 2007).

Based on the criteria established by the AASM (2007), the human sleep electroencephalogram can be subdivided into two fundamentally distinct phenomena, rapid eye movement (REM) sleep and non-REM (NREM) sleep, which alternate in typically five approximately 90 – 120 minute ultradian cycles over the course of a normal night's sleep. The NREM cycles may be further subdivided also according to AASM (2007) criteria into N1, N2 and N3 sleep stages, each occupying an arbitrary 20 or 30 second window of the sleep EEG recording called an epoch. Sleep is tightly regulated by circadian and homeostatic processes, which have been modeled in the two-process model of sleep regulation shown in **Figure 1.1** (Borbély 1982). This model describes a homeostatic process S and a circadian process C. A third ultradian process occurs within sleep and is represented by the alteration between REM and NREM sleep (Borbély and Achermann 2000). A homeostatic component has been shown in mammals of several orders (Tobler 2000). Sleep homeostasis has been defined as "the coordinated physiological processes which maintain most of the steady states in the organism" (p. 377) and the term sleep-homeostasis in particular refers to those mechanisms that counteract deviations from an average reference level of sleep, thereby augmenting sleep propensity after sleep has been restricted or deprived, reducing this propensity once sleep is initiated (Borbély and Achermann 2000). The principle marker of process S is SWA, which has been experimentally shown to increase as a function of prior wake (Borbély and Achermann 2000). Slow wave activity is characterized by the slow wave, a sinusoidal wave form oscillating at a frequency of 0.5 to 4.5 Hz with a minimum peak-to-peak amplitude of 75 uV. On a neurophysiological level, the slow-wave reflects the synchronous activity of hundreds of thousands of pyramidal neurons in the cortex as they initiate synaptic potentials in relative unison. Slow wave activity peaks during the first NREM cycle and can be enhanced by sleep deprivation (Borbély 1982). Process C is analogous to a clock, such that it determines the timing of opportunity for sleep to occur (Borbély 1982) and can be set by various means, which are termed *Zeitgebers*, the principle of which is light energy, which demonstrably suppresses melatonin secretion in humans, the primary neuro-hormone corollary of process C (Lewy et al. 1980) although many processes (e.g., alertness, core body temperature, gene expression, cortisol secretion among many others) follow circadian regulation (Lockley et al. 2007). Photons are transduced exclusively in the eyes by melanopsin containing retinal ganglion cells along a dedicated pathway, the retinohypothalamic tract, to the optic chiasm at the ventral hypothalamus and to a cluster of several thousand specialized cells called the suprachiasmatic nucleus (SCN) (Lockley et al. 2007). This impulse effectively resets the clock.

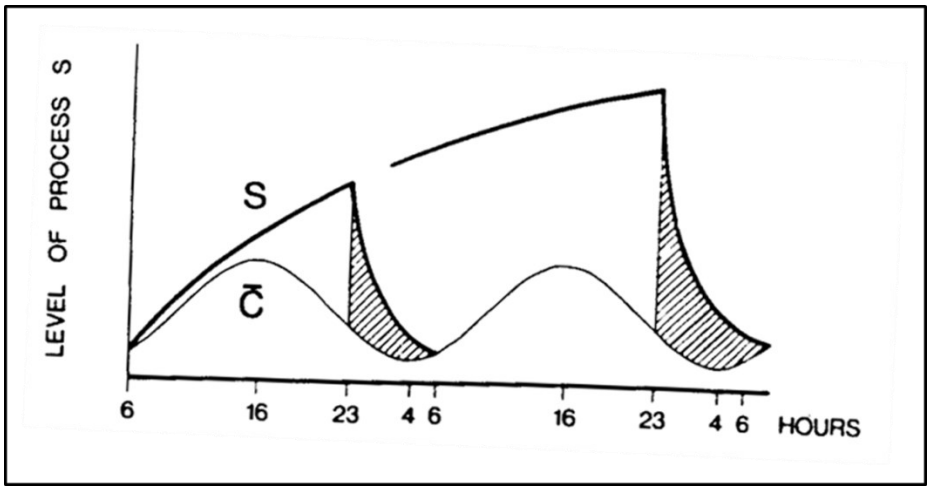

Figure 1.1 The two process model of sleep-wake regulation (Borbeléy, 1982). The time course of sleep processes after regular a waking time period (left side of plot) as well as after an extended waking time period (right side of plot) is shown. The level of process S and C (with overbar indicating the negative function of process C) are displayed. The vertical axis indicates level of process S and C. Horizontal axis indicates clock time in hours. Hatched areas show exponential decline of process S following initiation of sleep.

1.2 Chronotype

A broad array of physiological processes, such as regulation of body temperature and cortisol (Bailey and Heitkemper 2001), melatonin (Lack et al. 2009), catecholemines (Turton and Deegan 1974), in addition to processes related to cognition (Schmidt et al. 2007) is influenced by endogenous circadian rhythms. There is systematic variance between individuals, however, with respect to the phase position and period of the circarian rhythm of these respective variables as well as simple diurnal preference, and this systematic inter-individual variance can be characterized as chronotype (Roeser et al. 2012).

As Horne and Östberg (Horne and Ostberg 1976) have pointed out, this characterization, i.e., trait-like inter-individual variability in preferential management of rest-activity behavior as a function of endogenous circadian rhythm has been systematically investigated since the work of Freeman and Hovland (1934) and the work of Kleitman (1939); although the concept of "Morningness" and "Eveningness" dates back to O'Shea (1900), more than a century ago. In the interim, this work has been expanded upon (Adan et al. 2012; Cavallera and Giudici 2008; Kerkhof 1985; Tankova et al. 1994), and individuals reporting different chronotype have been examined with respect to objective biological markers of their circadian system, such as oral temperature rhythm (Horne et al. 1980), melatonin (Lack et al. 2009), cortisol and rectal temperature (Bailey and Heitkemper 2001), combined melatonin and rectal temperature (Duffy et al. 1999) as well as wrist-activity (Thun et al. 2012).

These findings corroborate subjective self-assessment by means of questionnaires, such as principally and originally (1976) the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ), although a variety of other questionnaires exists (Adan et al. 2012), such as the Circadian Type Scale of Folkard and colleagues (1979), the Diurnal Type Scale (DTS) of Torsval and Åkerstedt (1980) and the Munich Chronotype Questionnaire (MCTQ) by Roenneberg and colleagues (2003). There is also a drastically shortened version of the conventional Horne-Östberg MEQ available, the Horne-Östberg Morningness-Eveningness Questionniare – A Reduced Scale (rMEQ), developed by Adan and Almirall (1991), which has demonstrated strong correlation ($r = 0.69 – 0.90$) and sufficient convergent validity with the MEQ (Adan and Almirall 1991) and is comprised of only 5 (items 1, 7, 10, 18 and 19) of the original 19 question items, thus appreciably diminishing the burden for respondents (Adan et al. 2012; Caci et al. 2009; Chelminski et al. 2000). It has, moreover, demonstrably succeeded in discriminating between morning and evening chronotypes with the objective measure of wrist-activity (Natale et al. 2006a; Natale et al. 2006b). The format of the MEQ (Horne and Ostberg 1976) and rMEQ (Adan and Almirall 1991) consists of questions and scales, which assess preference for the timing of various behaviors (e.g., alertness, appetite, among others) in plain language, e.g., "How alert do you feel during the first half hour after having woken in the morning?", with responses ranging from "Not at all alert" to "Very alert", each awarded a value, and these values are summed to yield a total score reflecting degree of morningess or eveningness. The rMEQ (Adan and Almirall 1991) produces a range of scores yielding five chronotype categories: Definitely Morning Type (22 – 25); Moderately Morning Type (18 – 21); Neither Type (12 - 17); Moderately Evening Type (8 – 11); Definitely Evening Type (4 – 7).

On a basic behavioral level, individuals who may be categorized as evening types typically retire significantly later in the evening and awaken later in the morning compared to those categorized as morning types, who prefer earlier bedrest and rise times (Adan et al. 2012). In addition, differences in performance are detectable between evening and morning type individuals, such that cognitive and physical performance peak toward the end of the day among evening types, whereas this peak is evident in the earlier part of the day among morning types (Adan et al. 2012). The difference in the various parameters of either behavioral or biological-chemical can vary appreciably between the types, such that a difference of as much as 12 hours can be observed between the extreme ends of the morningness-eveningness spectrum for a given variable (Adan et al. 2012). The distribution of the various chronotypes is not equal and has been estimated to be ca. 40% of the adult general population characterized as evening type, 40% as morning type, with the remaining 60% being neither type (Adan et al. 2012).

With respect to the size of differences observed between morning and evening types, summarizing evidence regarding phase position in an early review of the literature, Kerkhof (1985)

noted that typical phase difference in body temperature between the two chronotypes corresponds to about two hours, whereas for alertness a 171 minute difference was observed; typical phase difference for sleep timing resides between these two with 80 minutes.

Various factors verifiably influence an individual's chronotype (Adan et al. 2012), such as age (Diaz-Morales and Parra-Robledo 2018), whereby individuals typically shift to morningness after adolescence; adolescence is itself, however, characterized by pronounced inclination toward eveningness and this observation has distinguished it enough from other developmental stages as to be considered a biological marker of adolescence (Roenneberg et al. 2004). Sex impacts chronotype, such that a greater proportion of evening types has been observed in males compared to females, and vice versa, although there is some ambiguity due to contradictory findings (Adan et al. 2012). Differences in circadian period length, possibly related to the menstrual cycle, have been observed (Adan and Natale 2002); a finding corroborated by the fact that sex differences vanish after menopause (Roenneberg et al. 2004). More evening types have been found among adolescent males than females, and sex differences begin at puberty and endure until approximately age 30 (Randler et al. 2017).

Much attention has been devoted to the investigation of chronotype due to its potential relevance to populations engaging in shift work (Adan et al. 2012), and it has long been hypothesized that some appreciable proportion of inter-individual variability with respect to an individual's suitability for shift work may be attributable to chronotype (Ostberg 1973; Vetter et al. 2015). Vulnerability to disease or poor health conditions, such as obesity and sequelae, e.g., type 2 diabetes (Hittle and Gillespie 2018), attributable to shift work emphasizes the urgency of understanding why some individuals are vulnerable, whereas others are not (Saksvik et al. 2011).

There is, however, presently no absolute consensus on which chronotype is best suited to undertake which type of shift work (Adan et al. 2012), and shift work styles vary probably as much as do individuals in their preferences for working them, such that thousands of varieties (e.g., chronicity, duration of shift, timing of shift, length of rotation, speed of rotation, direction of rotation, placement of intervening rest days, etc.) of shift schedules prevail throughout the world (Folkard 1992). Moreover, as Folkard (1992) argues, simply because an individual's chronotype 'matches' the hypothetically 'most suitable' shift for that individual to work, other enduring attributes or external influences are at least equally and perhaps very likely more relevant for that individual, and may repel them from volunteering for a given shift type proposed as 'most suitable' for them based on chronotype alone, or in the event they accept, there is no guarantee that they will ultimately successfully adjust to it. Nevertheless, there is some evidence that evening type is favorable to night work, whereas morning type favors earlier shifts (Hittle and Gillespie 2018), and limited evidence indicates that individual workers benefit when shift work correlates with their chronotype , thereby

reducing circadian disruption on sleep duration and quality (Juda et al. 2013) as well as on mental health (Vetter et al. 2015).

A variety of diurnal cardio-autonomic endpoints, such as heart rate (HR) (Kräuchi and Wirz-Justice 1994a), heart rate variability (HRV) (Scheer et al. 2010) and possibly also blood pressure (BP) (Millar-Craig et al. 1978; Scheer et al. 2010) but see (Kerkhof et al. 1998; Van Dongen et al. 2001), follow an evoked endogenously regulated circadian rhythm. Individual differences in the period, peak and nadir of these rhythms has led to investigation (Nebel et al. 1996; Roeser et al. 2012; Willis et al. 2005) of the role of chronotype in the management of these and associated endpoints. Nebel and colleagues (1996) undertook an investigation of healthy individuals and those with coronary artery disease (CAD), both of which samples were all male and characterized for morningness and everningness. These investigators (1996) could identify that morning type individuals displayed greater levels of cardiovascular activity, i.e., HR, systolic and diastolic blood pressure (SBP, DBP, respectively), in the morning hours, whereas evening type individuals displayed greater levels during the afternoon. They suggest that morningness and eveningness interact with time of day to evoke different circadian patterns. A stress task in this study induced greater cardiovascular stress response with a physical grip task and mental arithmetic task, such that an interaction was observed between time of day (07:00 vs. 12:30) and chronotype (morning type vs. evening type), with each chronotype displaying higher values of HR and rate pressure product (RPP; HR × SBP) at a time of day incongruent to their own diurnal preference. A subsequent study by Willis and coworkers (2005), which also investigated stress reactivity in cardiovascular variables, this time in both men and women, replicated the finding by Nebel and coworkers (1996), such that significant effects were observed in HR and SPP as a function of chronotype, whereby morning type individuals showed higher values in the morning, whereas evening types showed the opposite, with greater values in the afternoon. Roeser and colleagues (2012) included heart rate variability (HRV) in an investigation of chronotype in women which also measured HR and BP in the morning or afternoon. In this study, it could be shown that morning types had lower HR, DBP but higher vagal HRV compared to evening types. In this sample, morning types also slept better, smoked at a lower frequency and engaged in more physical activity in comparison to evening types (Roeser et al. 2012).The time of day and chronotype interactions present in the previous reports by Nebel and colleauges (1996) and Willis and colleagues (2005) could notably not be reproduced, however.

In conjunction with the stress reactivity findings of the two preceding papers (Nebel et al. 1996; Willis et al. 2005), Roeser and coworkers (2012) argue that HRV acts not only as an indicator of an individual's propensity to successfully regulate physiologically demanding tasks but also tasks requiring regulation of emotional and cognitive processes, citing the neurovisceral integration model of Thayer and coworkers (2009). Briefly, this model describes the integration of the cortex, its

activation in various cognitive tasks, and HRV as an index of this activation (Thayer et al. 2009). Individuals, for instance, with greater vagally mediated HRV outperform others on executive function tasks in an expansive variety of situations, the guiding hypothesis of which is that HRV is an index of prefrontal neural function. Within the context of the Roeser and collaborators study (2012), prefrontal cortical inhibition of the amygdala is hypothesized to be associated with greater vagal influence on HR. The greater the stress demand of the task at hand, the greater the prefrontal cortical inhibition required to suppress sympathetic activation of HR. Heightened executive functioning is accompanied by higher vagal activation and lower HR but higher HRV. Decreased vagal HRV has been found to accompany maladaptive coping strategies and heightened negative emotional arousal to stress (Appelhans and Luecken 2006) and a variety of disorders, which include sleep problems (Bonnet and Arand 1998), general anxiety disorder (Thayer et al. 1996), panic disorder (Friedman and Thayer 1998), depression (Rechlin et al. 1994) as well as posttraumatic stress disorder (PTSD) (Cohen et al. 2000). The link between the model of visceral integration and chronotype is forged by observations which include greater susceptibility to stress among evening types, who may also be less emotionally stable and suffer a greater prevalence of psychosomatic complaints and findings (Nebel et al. 1996; Willis et al. 2005) showing greater cardiovascular stress reactivity in chronotypes at a incongruent time of day.

The observation that individuals afflicted with various mental illnesses, such as mood disorders (Chung et al. 2012), alcohol use (Ishihara et al. 1985; Mazri et al. 2020) possibly among adolescents in particular (Hasler et al. 2017a; Hasler et al. 2017b) and PTSD (Hasler et al. 2013), are frequently evening types has led to investigation into individual differences in disease attributable in part to chronotype (Kivelä et al. 2018). A limited amount of research has focused specifically on PTSD in this regard, and these emergent findings (Hasler et al. 2013; Yun et al. 2015) indicate that evening chronotype might be a vulnerability factor for development of this tenacious memory disorder. One study (Yun et al. 2015) showed that evening type individuals reported significantly more PTSD symptoms in a sample of 515 Korean firefighters and emergency workers. In this study (Yun et al. 2015), evening type was associated with poorer sleep quality, greater depression and higher PTSD scores compared to morning and neither type. These authors (Yun et al. 2015) speculated that differences in personality, alcohol use and stress-management characteristics may contribute to their findings in addition to clock genes. Hasler and colleagues (2013) investigated affective dysregulation and sleep disturbances, such as nightmares (a hallmark intrusive memory symptom of PTSD) and insomnia, in a sample of 36 individuals with prior combat exposure and PTSD symptom severity to varying extents. In an ambitious study examining both behavioral and neural factors (positron emission tomography; PET) during waking and rapid eye movement (REM) sleep, they could demonstrate that eveningness was linked to greater lifetime PTSD symptomatology,

worse sleep quality and more intense nightmares of greater frequency. With respect to brain-based findings, eveningness was associated with increased activity in posterior cingulate cortex and the precuneus, in addition to brainstem regions, and not in prefrontal cortical regions as originally hypothesized in that report. This occurred during wakefulness as well as in REM sleep in these regions, which are also partially involved in arousal and REM sleep initiation (Hasler et al. 2013). These authors (Hasler et al. 2013)discussed the possibility that evening type individuals with PTSD may experience greater hyperarousal and this could possibly lead to problems initiating and maintaining sleep due to worry about personal safety or nightmare before sleep is initiated. This arrangement may lead to later sleep timing preferences and mask true chronotype, i.e., these individuals are not true evening types. More research is warranted on the putative relationship between PTSD and chronotype.

A broad array of physiological processes is influenced by circadian rhythms. Systematic variance between individuals in the phase position and period of the circarian rhythm as well as simple diurnal preference has led to the notion of chronotype, which has historically been assessed with a variety of questionnaires, the most frequently used of which is the Horne-Östberg Morningness-Eveningness Questionnaire and has been validated against a variety of biological rhythms. Summary review of literature on chronotypes indicates that the difference between the phase a given physiological endpoint or behavior of morning and evening types is appreciable (> 60 minutes). Chronotype is influenced by age among other factors. Whereas no consensus in the literature is discernable, there seems to be general support for individuals undertaking shift work whose chronotype is best suited for that given shift. Cardiovascular reactivity to stress may be exacerbated when physical or psychological stressors are encountered at times incongruent to an individual's chronotype. Under normal conditions, i.e., non-shift work, evening types appear to be at greater risk for a variety of psychological illnesses, such as affective disorders, and according to the visceral integration model, diminished vagal HRV is indicative of poor cognitive suppression of sympathetic autonomic response to stress and may underlie differences between evening and morning types. Evening type may contribute to vulnerability to PTSD, and the sleep of evening type individuals with a PTSD diagnosis may be of poorer quality than afflicted morning types. Chronotype represents a potentially significant and meaningful factor underlying individual differences in health and disease, which should be investigated further, particularly in at-risk populations, such as those exposed routinely to trauma and stress engaging in shift work professions.

1.3 The heart and cardiac-autonomic endpoints

The human heart is a marvel of nature. Its activity is nearly ceaseless and is an organ of vital importance. The heart contracts an average of 75 times per minute, 108,000 times per day and almost 40 million times per year. The heart will beat nearly 3 billion times in the lifetime of the average 75-year-old. The heart is comprised of 4 major pumping chambers, each of which ejects approximately 70 mL of blood per contraction in a resting adult. Thus, about five and a quarter liters of blood are pumped per minute, 14,000 per day and 10,000,000 per year. The purpose of the heart is to sustain life by pumping nutrient rich blood to the trillions of cells in the human body through a network of blood vessels, such as veins, arteries, venules, artierioles and capillaries that, along with blood and the heart itself, constitute the cardiovascular system. The blood is also crucial for the removal of waste materials, the immune defense of the body, the transport of oxygen, the distribution of heat and the maintenance of homeostasis (Betts et al. 2017).

The heart is located in the mediastinum within the thorax, medially between the lungs. The heart is about the size of a fist and its shape can be compared to that of a pine cone. It weighs between 250 and 350 g and consists of two atria, which are the upper receiving chambers for returning venous blood, and two ventricles, the chambers which account for most of the volume of the heart and are located beneath the atria. The ventricles pump blood into the lungs and arteries. Cardiac circulation can be divided into two circuits, the *pulmonary* circuit and the *systemic* circuit. Both transport blood. The pulmonary circuit pumps blood to and from the lungs to facilitate collection of oxygen and delivery of carbon dioxide to be exhaled. The systemic circuit pumps oxygenated blood to virtually all bodily tissues and transports relatively deoxygenated blood and carbon dioxide for subsequent pulmonary circulation. The cardiac cycle comprises ventricular contraction (systole) and ventricular relaxation (diastole). Blood pressure peaks during systole, as contraction of the left ventricle ejects blood from the heart. Blood pressure is lowest during diastole, as the left ventricle relaxes. The two primary components of the dynamics of blood flow (hemodynamics) are heart rate and stroke volume. Stroke volume describes the beat-to-beat volume of blood pumped from the left ventricle (Betts et al. 2017; Shaffer et al. 2014). The heart is composed primarily of muscular tissue termed the myocardium, which surrounds the four ventricles. The graceful and sophisticated swirling pattern of the myocardium resembles a figure 8 and permits the heart to pump blood more effectively than a linear pattern. Four valves, the tricuspid, bicuspid, aortic and pulmonary (semilunar valves), facilitate unidirectional blood flow through the heart. The two familiar heart sounds (S1 and S2) are generated when the right ventricle contracts (S1) and when the semilunar valves close (S2) during ventricular diastole (Betts et al. 2017).

The cardiac muscle exhibits some unique characteristics which distinguish it from both skeletal muscle and smooth muscle. The most exceptional of which is the property of autorhythmicity or the ability to spontaneously induce an electrical potential at a fixed rate (Betts et al. 2017). This electrical potential spreads rapidly across the cells of the myocardium in a coordinated and non-random pattern and triggers its contractile mechanism, an effective and concerted systole (Reisner et al. 2006). In the healthy heart, each heartbeat is initiated by an action potential, which originates from one of two primary internal rhythmic pacemakers, the sinoatrial (SA) node and the atrioventricular (AV) node (Reisner et al. 2006; Shaffer et al. 2014). Remarkably, these nodes continue to initiate action potentials in the absence of all efferent input from the cardiac autonomic nervous system, such that even upon removal of the heart from the chest cavity in transplantation scenarios it continues beating for several minutes. The SA node is the heart's primary pacemaker and consists of a cluster of cells specialized for conduction. It is located in the superior and posterior walls of the right atrium near the opening of the superior vena cava. The AV node is the second such dedicated cell cluster of the heart and is found in the inferior portion of the right atrium in the atrioventricular septum. The SA node and AV node serve as pacemakers and have intrinsic rates of 60 – 100 and 40 – 60 action potentials per minute, respectively. The myocardium itself has a rate of 20 – 40 action potentials per minute (Reisner et al. 2006). This intrinsic rate is controlled by the atomic nervous system (van Boxtel et al. 2018) in a manner which will be elaborated upon below. The relatively speedy rate of the SA node prevents the interference of slower parts of the heart's conduction system, such as the myocardium, in the generation of competing action potentials to maintain rhythmicity. The AV node can substitute the SA node in the event that the latter is injured or diseased (Shaffer et al. 2014), such as is the case in third-degree or total heart block. Once initiated in an individual cell, propagation of an action potential continues along the cell membrane until complete depolarization is achieved. This potential is then transmitted to the tightly coupled adjacent cells of the myocardium via the direct spread of ionic currents through low resistance connections, termed gap junctions, and importantly not via electrochemical synapse. Thus, the heart behaves electrically as a functional syncytium, and an impulse that is generated will propagate without regard to its place of origin throughout the heart and result in concerted mechanical contraction (Reisner et al. 2006). Action potentials initiated at the SA node propagate through the atria and ventricles from right to left but are prevented from crossing the atrioventricular junction by an electrical barrier between these chambers. This barrier is overcome at the AV node, a structure within the muscle wall between the two atria consisting of a tissue dedicated to the delayed conduction of action potentials. The AV node induces a critical pause in electrical transmission of the potential, which is in part attributable to the small size of the AV cell bodies, which decelerate the speed of the impulse. This approximately 100 ms pause is critical for heart function, as it allow the cardiomyocytes of the atrium to finish their contraction that pumps blood to

the ventricles before the impulse propagates to the cells of the ventricles. Action potentials then pass through the AV node and are conducted via the bundle of His and then to the fascicular apex of the bundle branches to the Purkinje fibers, thereby causing the myocardium of the ventricles to contract (van Boxtel et al. 2018).

Despite the heart's unique property of autorhythmicity, HR is modulated by the Autonomic nervous system (ANS) from a major cardiovascular center in the medulla oblongata of the brain stem. The ANS regulates the body's internal environment to sustain homeostasis (Porges 1995). Sensory information from proprioceptors, chemoreceptors and mechanoreceptors (baroreceptors) in the heart, in addition to information in the cerebellum and limbic system, is integrated in the medulla (Shaffer et al. 2014). The ANS is critically involved in the regulation of the cardiovascular system and can be divided further into two anatomically distinct branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). These project to most organs and exert opposing effects (van Boxtel et al. 2018). Under normal conditions, a dynamic relative balance is struck between the SNS and PNS, which contributes to autonomic tone (Shaffer et al. 2014). Sympathetic stimulation of the heart has the effect of progressively increasing heart rate with a delay of approximately 5 sec from initial stimulation. Parasympathetic stimulation, in contrast, induces a decrease in HR almost instantaneously (Shaffer et al. 2014).

The SNS is roughly characterized by the epithet "fight-or-flight" and commands the body's defensive response to perceived threat, although there are exceptions to this. In an encounter with a perceived threat, greater amounts of oxygen must be inhaled and delivered efficiently to skeletal muscles in order to enhance physical performance and subsequently increase the survival chances of an organism. The SNS coordinates this by increasing heart rate (HR) and blood pressure (BP), dilating blood vessels in skeletal muscles and dilating the bronchi of the lungs to increase air exchange. Additionally, pupils dilate to improve vision and sweat glands become active to cool the body. The SNS simultaneously inhibits the digestive system, such that blood can be dedicated to the delivery of oxygen to skeletal muscles instead of absorbing nutrients (Betts et al. 2017).

The SNS must coordinate a vast array of responses in diverse organ systems and tissues from a finite anatomical region in the central nervous system, the cardioaccelerator center of the medulla, via the neurons of the thoracic and upper lumbar spinal cord (T1 to L2), to effect systemic change. Efferent pre-ganglionic fibers originating at a central neuron in the lateral horn project to ganglia next to the vertebral column via ventral spinal roots. Post-ganglionic fibers then proceed to enervate target organs. Efferent fibers from the cervical ganglia and the superior thoracic ganglia (T1-T4) enervate the heart and increase heart rate via norepinephrine (NE) release and binding to the beta-adrenergic (β1) receptor. Release of NE has the effect of shortening the repolarization period of cardiomyocytes,

thereby increasing the rate of depolarization, ventricle contraction and consequently heart rate (Betts et al. 2017).

The PNS is characterized by functions related to "rest-and-digest," although this is an oversimplification. The PNS is named for its lateral proximity to the thoracolumbar region of the spinal cord and also bears the designation craniosacral system, since its preganglionic neurons are found within the nuclei of the brain stem and lateral horn of the sacral spinal cord. The cardioinhibitor center of the medulla governs PNS stimulation of the heart. Stimulation proceeds via the vagus nerves to the SA node, the AV node and the atrial myocardium, where acetalcholine is released at the neuromuscular junction, binding to muscarinic (primarily M2) receptors to slow the heart by decreasing the rate of depolarization (Betts et al. 2017; Shaffer et al. 2014). The principal connections of the PNS resemble those of the SNS with a few differences. Preganglionic fibers from the cranial region proceed in cranial nerves, whereas those fibers of the sacral region proceed in spinal nerves (Betts et al. 2017). The PNS dominates during rest and results in a mean HR of 75 beats per minute (bpm), although it can also slow the heart to as low as 20 or 30 bpm or temporarily stop it from beating (Shaffer et al. 2014). The SNS and PNS have distinct patterns of activity during sleep (Trinder et al. 2012), a topic which will be addressed in subsequent sections.

The performance of the heart, in essence a pump, depends primarily on the contraction and relaxation capabilities of the myocardium, although other factors impinge on performance, such as the organization of myocardial cells, coronary delivery of oxygenated blood to cardiac tissue, the properties of this tissue itself, as well as the heart's electrical rhythm and valve function (Reisner et al. 2006). Moreover, alcohol (Spies et al. 2001), smoking (Dinas et al. 2013), medications (Buckley and Sanders 2000), age (Kostis et al. 1982), physical fitness (Jensen et al. 2013), and sex (Yamasaki et al. 1996) can alter heart performance appreciably (Clifford 2006). The average resting heart rate of a healthy adult is 75 bpm, whereby the range is 60 - 100 bpm. During sleeping the mean resting heart rate of a healthy adult is 40 - 60 bpm, although HR changes significantly as a factor of sleep stage and the circadian system (Trinder et al. 2001). Women have higher mean resting HR than men (Koenig & Thayer, 2016). Age influences mean resting heart rate, such that newborn children have a resting HR of 120 bpm. HR steadily decreases into adulthood, such that male individuals ages 6 – 11 have a mean resting HR of 79 bpm, whereas for male individuals age 20 – 39 it is 67 bpm and in age 60 – 79 it is 64 bpm. For female individuals, the mean resting HR values in these same age groups are 83, 71 and 68 bpm, respectively (Statistics Canada 2011). Peak HR is around 200 - 220 bpm for a healthy adult, and this diminishes as one ages, such that maximum HR in a 60-year-old is typically 160 bpm. Physical fitness powerfully impacts mean resting HR and maximum HR, such that the mean resting HR of trained athletes is around 50 bpm (Herzig et al. 2018a). Umetami et al. (1998) report a decrease in HR with age, but at a slow rate and decade-by-decade (10-99 years) comparisons did not

reach significance. Female HR was significantly higher than HR in age-matched males <50 years of age, after which age, sex differences vanished. HR declined significantly within females, whereas HR was not affected by aging.

HR measurement is a convenient, non-invasive technique for the assessment of general cardiovascular fitness. Faster resting HRs during waking are associated with higher BP, and this is evident across the entire range of BPs among the general population for any age group, although this association is stronger for systolic than diastolic BP and may be stronger among men than women (Palatini and Julius 1997). Resting HR obtained at the clinic during waking has prognostic value for patient health and has been shown to correlate with subclinical markers of cardiovascular damage and independently predicts cardiovascular morbidity, mortality and all-cause death (Cuspidi et al. 2018). The strength of the evidence indicates that HR alone is sufficient to estimate risk for adverse cardiovascular events.

All aspects of the human cardiac autonomic nervous system, such as systolic and diastolic BP (Millar-Craig et al. 1978) and mean HR (Hilton et al. 2000; Vandewalle et al. 2007), display robust diurnal rhythms (Vandewalle et al. 2007) and are lower during sleep than wakefulness with perhaps the notable exception of during REM sleep, when HR levels can approach or exceed those of waking (Trinder et al. 2012). Blood pressure may not follow an evoked circadian rhythm under constant routine conditions (Kerkhof et al. 1998; Van Dongen et al. 2001). Such diurnal variation is evident in common cardiovascular diseases, such as ischemic stroke (Gupta and Shetty 2005), heart attack and cardiac death, with onset occurring typically in the late morning hours, i.e., 06:00 – 12:00 (Cohen et al. 1997b; Elliott 1998). Irregularities in cardiovascular function associated with disease risk are not limited to the morning hours, however. Adverse cardiovascular consequences are associated with circadian misalignment, as evidenced by the increased risk for cardiovascular and metabolic disease associated with shift work scenarios (Scheer et al. 2009). Individuals whose BP does not follow the normal 24-hour rhythm are at greater risk for stroke (O'Brien et al. 1988).

The nocturnal drop in cardiovascular tone, which is referred to as a "dip," defined as a 10% to 20% reduction in mean systolic pressure during sleep compared to waking (Bloomfield and Park 2015; O'Brien et al. 1988), indicates normal cardiovascular functioning. Dips less than this, i.e., blunted or absent dips, are prognostic of an adverse cardiovascular event (Eguchi et al. 2009) and all-cause mortality (Ben-Dov et al. 2007). Women with posttraumatic stress disorder (PTSD) diagnosis who did not dip compared to those who did slept worse, endorsed more traumatic event categories, poorer daytime functioning and longer sleep latencies (Ulmer et al. 2013). There may be a relationship between PTSD and sub-threshold PTSD with nondipping in African American males (Mellman et al. 2009).

Dipping is conventionally assessed by measuring systolic blood pressure (O'Brien et al. 1988). A limited number of studies (Ben-Dov et al. 2007; Cuspidi et al. 2018; Eguchi et al. 2009; Verdecchia et al. 1998) have, however, investigated the prognostic value of a blunted decrease of nocturnal HR in the general population and could confirm HR as a reliable alternative to BP. In fact, in one study (Ben-Dov et al. 2007) conducted in a clinically heterogeneous sample of 3,957 patients, the HR dip, once adjusted for covariates, actually predicted all-cause mortality slightly better than systolic BP. In these studies, the same threshold of < 10% dip in BP is applied to HR.

Utilizing HR – as opposed to BP – for assessment of nocturnal dipping during sleep has the obvious advantage of minimally interfering with the individual's sleep, since electrocardiogram (ECG) electrodes or photoplethysmography (PPG) can be used, which do not require the repeated activation of pressurized cuffs for data collection, as is the case with conventional BP measurements. Commercially available wearable devices, such as the wristwatch-like Fitbit Charge 2^{TM}, with built-in PPG capabilities, have flooded the market and represent a popular and affordable means of conveniently collecting HR data during sleep or around-the-clock (de Zambotti et al. 2019; de Zambotti et al. 2017). Moreover, assessment of cardiac activity by means of ECG belongs to the American Academy of Sleep Medicine's (AASM 2007) recommended parameters for the scoring of sleep and associated events and is a longstanding routine measurement in most sleep laboratories. There is a paucity of research dedicated to the investigation of cardiovascular variables during sleep (Silvani and Dampney 2013). Thus, a vast amount of ECG data is collected, yet the majority of which goes unanalyzed. Given these considerations, it becomes apparent that HR measurement during sleep represents a promising non-invasive and cost-effective means of assessing cardiovascular variables in a timely and convenient manner. Sleep laboratories could begin analyzing huge amounts of data that has already been collected yet languishes in data bases to answer pressing questions on sleep and cardiovascular function as it pertains to cardiovascular risk (Silvani and Dampney 2013; Stein and Pu 2012).

The cycle of depolarization and repolarization of the many thousands of myocardial cells of the heart, i.e., the cardiac cycle, generates electrical potentials which can be amplified and recorded by means of the electrocardiogram (ECG) (**Figure 1.2)**. The modern ECG typically involves the application of adhesive electrodes to the skin to record the bioelectric activity of the heart. The voltage difference is taken from between two electrodes or leads. The electrodes are arranged in standard configurations, usually on the torso and hips, adapted from the original configuration by ECG pioneer Dr. Willem Einthoven, who was awarded the Nobel Prize in physiology and medicine in 1924 for inventing the electrocardiograph (AlGhatrif and Lindsay 2012; van Boxtel et al. 2018). In the present study, two electrodes were utilized, one placed below the right clavicle and one between the ribs of the left rib cage (modified lead II configuration) according to American Academy of Sleep

Medicine (AASM 2007) standards. Once amplified and displayed on a computer monitor, the visual representation of the heart's bioelectrical activity in a healthy individual can be described as a sinus wave, whose constituent morphological features form a stereotypical complex consisting of a sequence of sharp peaks and valleys (van Boxtel et al. 2018). These peaks and valleys of the ECG are given the arbitrary alphabetical labels PQRST and are often illustrated on graph-paper, a longstanding tradition in cardiology harkening back to the days in which analyses were done by means of pen-and-paper (Reisner et al. 2006). The PQRST labels were selected by Einthoven to be in keeping with the mathematical tradition of Descartes, utilizing the terminal part of the alphabet sequence (AlGhatrif and Lindsay 2012). Electrical activity precedes myocardial contraction and is plotted in the PQRST complex as follows. Atrial contraction follows SA node depolarization and is represented by the P wave. The QRS complex in the ECG reflects depolarization of the ventricles and ventricular systole. The T wave represents repolarization of the ventricles following ventricular relaxation (Betts et al. 2017).

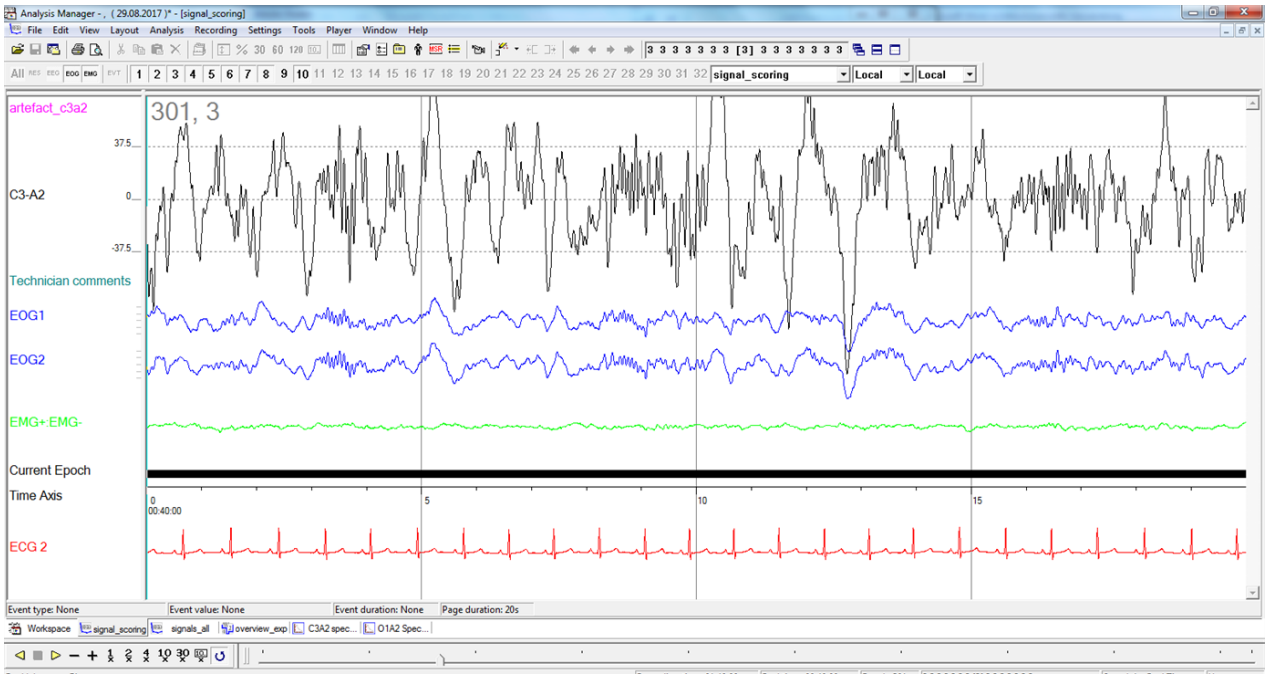

Figure 1.2 Typical polysomnographic display containing ECG trace in red ('ECG 2', bottom) during stage N3 sleep. The distinct 'P-Q-R-S' waveshapes can be evinced from this plot, whereby the R peak is the salient signal maximum, facilitating its simple and robust detection by computer algorithm.

The relevant question when assessing cardiac health should be, is the dynamic balance between PNS and SNS regulation of the heart appropriate for the given circumstances with which an individual is presently confronted (Shaffer et al. 2014)? For instance, is HR higher, reflecting SNS dominance, when engaged in a strenuous physical task, and is HR decreased, reflecting PNS dominance, when at rest (Shaffer et al. 2014)? Should the SNS dominate at rest times, e.g., during

sleep, then it may be an indication of abnormality, such as asymptomatic tachycardia, or disease, such as ischemia (Betts et al. 2017). Another way of conceptualizing appropriate regulation when confronted with environmental challenges is fitness. An inherent flexibility or resilience, i.e., the capacity to successfully adapt, characterizes healthy function within an individual's key regulatory systems (Shaffer et al. 2014).

Heart rate variability was possibly first formally investigated in association with fetal monitoring, where certain patterns, i.e., diminution in HRV signifying distress and imperative immediate delivery, were shown to precede fetal death (Hon and Lee 1963), and has emerged as a marker of cardiovascular disease, the leading cause of death and disability among both men and women (Thayer et al. 2010), particularly in developed countries (Yusuf et al. 2001). Insufficiently high HRV is associated with all-cause mortality, is a predictor of future health problems and has been associated with autonomic dysfunction (Shaffer et al. 2014). Deficient parasympathetic inhibitory processes, general autonomic imbalance and elevated environmental stress increase risk for cardiovascular disease and mortality (Thayer et al. 2010). Autonomic imbalance due to stress is implicated in PTSD, a patient population in which risk for cardiovascular disease is elevated compared to the general population (Coughlin 2011).

In patients with PTSD diagnosis, overall HRV and vagal tone was lower and HR was higher by about 10 bpm (Cohen et al. 1997a) and an autonomic hyperactivation at rest was observed as well as diminished autonomic response to a stressor compared to healthy controls (Cohen et al. 1998). Elevated resting HR (Blanchard et al. 1982; Buckley and Kaloupek 2001) is a hallmark correlate of PTSD, a disorder characterized by autonomic dysregulation and chronic hyperarousal (Buckley and Kaloupek 2001; Dennis et al. 2016; van Boxtel et al. 2018).

Because mean HR alone is insufficient to index autonomic control of the heart, it is necessary to look deeper, toward more complex patterns of heart function, such as subtle fluctuations in beat-to-beat intervals, termed RR intervals, which refer to the duration in time between individual normal R peaks of the fiducial QRS complex. The R peaks are detected conventionally by computer algorithm, e.g., RHRV (Rodríguez-Liñares et al. 2011). Such patterns reveal a highly variable heart rate, which reflects the influence of a number of processes, such as autonomic neural activity, BP, the respiratory system, the renin-angiotensin system and environmental factors, whose combined influence generates transient rhythms in heart function, which would go undetected if mean HR alone were to be considered (Shaffer et al. 2014). Importantly, however, evidence suggests that it may be necessary to correct for HR when assessing HRV, as HR is highly correlated with HRV and reflects the intrinsic HR generated by the SA node and not autonomic innervation, which may lead to misinterpretation of results when a guiding assumption that HRV reflects autonomic regulation only is assumed (Herzig et al. 2018a).

Heart rate variability presents investigators and clinicians with a window into cardiovascular health by means of quantifying the relative contributions of the SNS and PNS in the cardiac autonomic nervous system. Variables can be derived from RR intervals in either the time or the frequency domain and computed per desired unit time, typically 5 min (Kristal-Boneh et al. 1995), and in desired state, such as deep sleep, rest or during performance of a given cognitive or physical task (van Boxtel et al. 2018). A task force was assembled to standardize the methods in the field of HRV research and clinical its application and published a set of guidelines to these ends (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). All variables are computed from an inter-beat-interval (IBI) file generated by the ECG or PPG, which contains the RR data. The normal RR intervals may also be referred to as normal-to-normal intervals (NN intervals) or heart period (van Boxtel et al. 2018). They are termed "normal" because abnormal beats, i.e., those which do not originate from the SA node, such as ectopic beats arising from the myocardium, are excluded from analyses (Clifford 2006). A variety of computer programs is available to conduct HRV analyses, such as R, which is a free software environment, in which the freely available RHRV package can be run to perform HRV analyses (Rodríguez-Liñares et al. 2011).

A number of statistics are available in the time domain to assess HRV, such as the mean NN interval or the standard deviation of the NN interval (SDNN) measured in milliseconds, which reflect global HRV (Shaffer et al. 2014; van Boxtel et al. 2018). Low values of SDNN adjusted for age predict morbidity and mortality, such that greater SDNN value is associated with greater chances for survival (Kleiger et al. 1987). Time domain statistics are typically computed without resampling and for this reason are robust to appreciable data removal, which is frequently the case due to the presence of artifacts and ectopic beats in ECG and PPG recordings, which must be excluded (Clifford 2006). When longer, i.e., 24 hr, recordings are made, as is frequently the case in Holter monitor recordings, the SDANN can be computed, which is the standard deviation of all 5 min segments of NN intervals and is computed in milliseconds. It correlates highly with SDNN (Shaffer et al. 2014). An SDNN index may also be computed from all 5 min segments of a 24 hr recording. It is the mean of the standard deviations in each 5 min segment and is believed to reflect slow periodic autonomic influence on HRV (Shaffer et al. 2014; van Boxtel et al. 2018). The most common time domain statistic for short-term variation in HRV is the root mean square of successive differences (RMSSD) between normal heart beats in milliseconds and is the primary statistic used to estimate vagally mediated fluctuation in HRV and may reflect respiratory sinus arrhythmia (RSA), although this is still debated (Shaffer et al. 2014). The pNN50 statistic describes the percentage of adjacent NN intervals that differ by more than 50 ms over a recording of 24 hr duration; however, varying the value by x ms (e.g., 20 ms instead of 50 ms) enhanced discrimination between normal and pathological conditions

(congestive heart failure vs. normal heart function), state of consciousness (sleeping vs. waking) and age (adult vs. older adult), significantly (Mietus et al. 2002). The pNN50 correlates with RMSSD and may provide an estimate of RSA, particularly in older adults (Shaffer et al. 2014).

Frequency domain components are also available and bring with them some advantages over statistics calculated in the time domain, such that both frequency and amplitude are included over a given time interval. This relates variance (power) to specific frequencies, and values are expressed as power spectral density, which is the area under the curve (Shaffer et al. 2014; van Boxtel et al. 2018). Power spectral density can be calculated by either fast Fourier transformation (FFT) or by autoregressive methods. Both methods assume equidistant spacing in the time base (4 Hz is recommended), which requires that NN intervals be interpolated (typically by means of cubic spline) to a real time axis (van Boxtel et al. 2018). If total power is calculated, it will correspond to global HRV as captured by SDNN; however, if short recordings (e.g., 2 - 5 min) are used for analysis, then two statistics can be reliably computed, low frequency (LF; 0.04-0.15 Hz; period >7-25 s) and high frequency (HF; 0.15-0.4 Hz; period >7 s). The very low frequency (VLF; <0.04 Hz; period >25 s) can be computed for recordings as short as 5 min (van Boxtel et al. 2018); however, the Task Force (1996) discourages computing VLF for anything shorter, as its interpretation becomes dubious due to its fundamental nonharmonic component, which is affected by algorithms of baseline or trend removal.

The HF statistic reflects vagal activity and is referred to commonly as the respiratory band, since it corresponds to RSA. In RSA, HR accelerates as one inhales and decelerates as one exhales. This is due to inhibition of vagal outflow during inhalation by the medulla, resulting in acceleration of the HR (Shaffer et al. 2014). It should be noted that any rapid changes in HR, both acceleration and deceleration of HR, are vagally governed, since it is only the parasympathetic component of the cardiac autonomic nervous system that can exert instantaneous influence on HR and not the much slower (in the order of 5 s post impulse) sympathetic component. Whereas sympathetically driven HR increases are comparatively slower, they are the primary means by which HR is increased and the inertia is much greater, such that a single impulse can induce sustained HR increases lasting for 5 - 10 s (Hainsworth 1995). Steady levels are achieved after 20 – 30 s post sympathetic impulse. Vagal outflow is restored during exhalation, whereby the heart is then decelerated (Shaffer et al. 2014). Vagal effects on HR are fast yet transient due to the high proportion of acetylcholinesterase in the SA node, which results in the acetylcholine being quickly hydrolised. It is believed that vagal influence on the heart surpasses that of the sympathetic system through two independent mechanisms; one describes a cholinergically driven reduction in norepinephrine and another cholinergic reduction in response to an adrenergic stimulus (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Seminal experiments involving selective

pharmacological block of muscarinic receptors with glycopyrrolate and block of β-adrenergic receptors with propranolol in dogs (Akselrod et al. 1981) and atropine block of muscarinic receptors in humans (Pomeranz et al. 1985) implicate vagal mediation of the HF component, in addition to electrical electrostimulation of the vagus nerve (Kamath et al. 1992).

The LF band probably reflects baroreceptor (stretch-sensitive mechanoreceptors in the heart chambers, vena cava, carotid sinuses and aortic arch) activity - and not sympathetic innervation - during resting, caused by tissue distention from increases in BP, thereby modulating autonomic activity in the form of a feedback loop. The sympathetic rhythm seems maximally active at a frequency of 0.1 Hz, whereas the parasympathetic rhythm is actively involved in regulating HR as low as 0.05 Hz (Shaffer et al. 2014).

The relationship between SNS and PNS autonomic governance of heart function is perhaps less straightforward than competitive stimulation of SA node (Cacioppo et al. 1999), whereby an increase in one component implies a reduction in another, analogous to a zero-sum game (Shaffer and Ginsberg 2017). Orthostatic challenge may yield such reciprocal, seesaw-like patterns, i.e., sympathetic activation and parasympathetic withdrawal; however, exposure to a psychological stressor has been shown to yield activation of both the SNS and PNS in parallel (Cacioppo et al. 1999), as is also the case during sexual arousal, and both may be simultaneously inhibited, such as during anesthesia (Porges 1995). Moreover, reflexogenic variation of arterial BP in dogs by means of either intravenous infusion of a vasodilator (sodium nitroprusside) or a vasoconstrictor (methoxamine) under β-sympathetic or parasympathetic blockade induces increase in LF peak (Akselrod et al. 1981). Clearly, the actual system is far more complicated than what a dichotomous model would predict, and it is difficult to unambiguously interpret LF power in the absence of knowledge of the specific circumstances in which it is recorded, which individually may impact some combination of baroreflex, vagal or sympathetic mechanisms (Shaffer et al. 2014).

To overcome this considerable obstacle, investigators typically utilize the ratio of HF to LF power, termed the HF/LF ratio in estimating sympathetic innervation of heart function. Nevertheless, interpretation of the HF/LF ratio is itself not without controversy, as it too incorporates the LF component, and should be interpreted with caution and never in absence of the experimental conditions and the separate LF and HF components, from which the ratio is derived (Shaffer et al. 2014).

The VLF band is likely intrinsically generated by the heart and may be modulated by the sympathetic component. VLF power increases typically during the night and reaches its peak before awakening in the morning, which may correlate with the cortisol increase at that time. Long term single neuron recording from an afferent neuron in the dog heart shows that its electrostimulation results in the activation of feedback and feedforward loops within the heart's intrinsic nervous system,

the cardiac ganglia and the spinal column (Shaffer et al. 2014). The VLF is not affected by sympathetic blockade and is sustained in spinal cord injury such as tetraplegia, a clinical population in which cardiopulmonary SNS innervation is impaired (Hagen et al. 2012).

Finally, the ULF band can only be assessed in recordings minimally 24 h in length and reflects circadian oscillation in HR and likely thermoregulation, metabolism and the renin-angiotensin system. The clinical relevance of this band is as of yet undetermined (Shaffer et al. 2014; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

Despite the fact that exposure to stress and potentially traumatic events represents the norm in most countries (Kessler et al. 2017), most individuals maintain healthy psychological and physiological functioning after exposure (Ogle et al. 2013). Nevertheless, stress and trauma remain an important cause of psychopathology (e.g., acute stress disorder, PTSD, substance abuse disorder and depression) and are associated with considerable economic burden and tremendous human suffering (Kalisch et al. 2017; Kessler et al. 2017). Research has shifted progressively away from the study of susceptibility and pathology and toward the study of resilience and health over the past half of the twentieth century (Kalisch et al. 2017). Resilience can be operationally defined as the process of dynamic adaptation to a given stressful life circumstance to maintain mental health and cannot be understood in the absence of a potentially traumatic event (Kalisch et al. 2017). The question as to why it is that some individuals are resilient to psychological stressors, whereas other succumb to them and develop mental illness, is growing ever louder, and has driven researchers and clinicians into understanding individual differences that modulate resilience (Carnevali et al. 2018a). For instance, at a glance it is obvious that individual differences regarding age (Laird et al. 2019; Masten et al. 1990), sex (Tsirigotis and Łuczak 2018) and life circumstances (Ogle et al. 2013) modulate resilience propensity, a fact that is reflected in differential prevalence rates of trauma and stressor-related disorder diagnoses among these populations (Kessler et al. 2017). Evidence, furthermore, suggests that genetic (Breen et al. 2015; Niitsu et al. 2019) and epigenetic (Feder et al. 2009; Heinzelmann and Gill 2013) factors may also be instructive; race may be a factor (Herbert et al. 2018).

Whereas there is an abundance of subjective assessment tools available to index resilience to psychological stress, among others the Connor-Davidson Resilience Scale (Connor and Davidson 2003), reflecting the conventional focus on these self-report psychometric measures in the scientific study of stress resilience, the relative absence of objective measures becomes increasingly apparent after a brief survey of the literature (Carnevali et al. 2018a). Despite the inherent value in subjective measures, they are vulnerable to bias and manipulation, both intentional and unintentional, and should be accompanied by objective measures whenever reasonably possible. A lack of objective measures may, moreover, impede a holistic understanding of resilience, which should at a minimum incorporate

those physiological and morphological predictors putatively involved in susceptibility to stress arising from exposure to potentially traumatic events (Carnevali et al. 2018a). From a clinical standpoint, the identification of such biomarkers would theoretically benefit the development of novel treatment and prevention strategies, as well as monitoring approaches and may help to facilitate the early detection and timely treatment of trauma and stressor-related psychopathology (Carnevali et al. 2018a). One promising candidate biomarker that has emerged is the autonomic nervous regulation of the cardiovascular system, and in particular, the index of its function by means of heart rate variability (Carnevali et al. 2018a).

Shaffer, McCraty and Zerr (2014, p. 6) capture the essence of HRV and resilience succinctly in their description of a concert of intrinsic rhythms generated by the heart, which together "create a dynamic physiological control system that is never truly at rest and is certainly never static," that "remains responsive and resilient, primed and ready to react when needed." Others (Hildebrandt et al. 2016) emphasize the flexibility of concerted cardiac and brain activity in coordinating adaptive responses to the demands of a constantly changing environment and thus "enabling nuanced adjustments to behavior to match those demands" (p. 880), which is particularly crucial when survival depends on initiating a quick response in a dangerous situation. Indeed, as Porges (1995) points out, stasis is the opposite of homeostasis and can be defined as the absence of any endogenous dynamic variability, which, when present, indicates severe physiological compromise. Critically, the resilience concept incorporates not only the initial response to a stressor but recuperation thereafter, and evidence suggests that the ANS and the vagal component particularly, contributes significantly to one's capacity to respond to and recuperate from a stressful experience (Souza et al. 2007).

Empirical evidence linking HRV and resilience is mounting (Carnevali et al. 2018a). A relative absence of HRV is already considered by some (Beauchaine and Thayer 2015) to be a reliable transdiagnostic biomarker of psychopathology. Resting vagal indices predicted active resistance and recovery from mentally and physically stressful events (Dong et al. 2018), and the vagal HRV component (RMSSD) may be associated with cognitive flexibility when confronted with a threat (Hildebrandt et al. 2016). Certain cognitive feedback interventions and vagal HRV (HF) biofeedback as part of a military training program meant to boost resilience may benefit post-deployment PTSD outcomes (Pyne et al. 2019). A variety of hallmark individual characteristics and behaviors associated with resilience in adulthood (Carnevali et al. 2018a; Wu et al. 2013) have also been independently associated with high vagal HRV, such as optimism (Oveis et al. 2009), reappraisal (Williams et al. 2015), coping (O'Connor et al. 2002), social support seeking and self-regulation (Geisler et al. 2013), prosocial behavior (Bornemann et al. 2016; Porges 2007), and mindfulness (Svendsen et al. 2016). Physical fitness, furthermore, epitomizes the concept of stress resilience (Childs and de Wit 2014;

Deuster and Silverman 2013; Dienstbier 1989) and is simultaneously the definition of cardiovascular health (Blair 2009).

A small but growing body of literature suggests that HRV, and the vagal component of HRV in particular, may be a biomarker of psychological stress resilience (Carnevali et al. 2018a). Individuals showing higher resting vagal (RMSSD) HRV before experimentally induced psychological stress scored higher on a measure of ego resilience, displayed greater reduction in tachycardia during stress induction and recovered more efficiently than those individuals with lower resting vagal HRV (Carnevali et al. 2018a; Souza et al. 2013). This replicates findings in an earlier paper by the same group (Souza et al. 2007), which linked high relative vagal (HF) HRV with ratings of resilience. These findings are compatible with others showing an association of diminished pre-stress resting state vagal activity (RMSSD) and poor cardiovascular, endocrine and immune markers after exposure to stress (Weber et al. 2010). Further evidence showed a negative relationship between increased post-stress recovery time in a selection of cardiovascular variables (HR, pulse amplitude of the finger, pulse transmission times to both ear and finger and BP and scores of ego resilience (Tugade and Fredrickson 2004).

Longitudinal studies are indispensable in evaluating the potential predictive power of HRV on stress resilience, and although to date most research has utilized a cross-sectional design (Carnevali et al. 2018a), studies are emerging which take a longitudinal approach and have indeed shown that pre-stress vagal HRV measures indeed predict healthy outcomes (Yang et al. 2019), such as diminished risk of PTSD diagnosis (Minassian et al. 2015), PTSD severity (Pyne et al. 2016), depressive symptoms (Carnevali et al. 2018b) and decreased risk of cardiovascular morbidity (Treiber et al. 2003).

As Carnevali and coworkers (2018) succinctly summarize, a patter appears to be emerging, such that those individuals who perceive, and correspondingly rate themselves on questionnaires, as more resilient, tend to have speedier recovery from acute stress, are less likely to succumb to mental illness in the aftermath of stress and show greater resting vagal HRV than those with the opposite profile. Sleep, and particularly slow-wave sleep, provides investigators with an optimal window into vagally-driven cardiovascular function (Brandenberger et al. 2005a; Herzig et al. 2018a; Herzig et al. 2018b; Herzig et al. 2017a; Herzig et al. 2017b). In the following section, the role of sleep in cardiovascular regulation will be explored, with an emphasis on HRV and slow-wave sleep.

Sleep is a heterogeneous behavior, and regulatory control of the cardiovascular system is sleep-waking state dependent (Silvani et al. 2008; Trinder 2008; Trinder et al. 2012), as indexed by measures of HR (Trinder et al. 2001), HRV (Stein and Pu 2012), BP (Silvani 2008) and baroreflex sensitivity (Yang et al. 2019), which change significantly from waking to sleeping. Sleep can be arbitrarily divided into rapid eye movement sleep (REMS) and non-rapid eye movement sleep

(NREMS), which can be further divided into five stages, N1, N2, N3 (comprising NREMS), REM and waking (AASM 2007), which are typically 20-30 seconds in length. Sleep and waking behavior can be modeled as two processes, the circadian and homeostatic processes (Borbély 1982); however in this section, the focus will be directed toward the latter and will investigate the role of sleep in the regulation of cardiac autonomic activity.

Cardiovascular activity attenuates by 10% – 20% in sleep compared to waking, referred to as dipping (O'Brien et al. 1988), and when posture and sleep are controlled, this reduction is partially induced by postural change (Trinder et al. 2012); both the change from standing to supine position and sleep induce reductions of comparable magnitude, i.e., ca. 7 mmHg, in the case of BP. The reduction due to sleep is fully achieved after a period of approximately 30 minutes, and HR may fall more rapidly than BP (Carrington et al. 2005). This reduction endures throughout NREMS,increasing over the night gradually as a function circadian phase (Hilton et al. 2000), until dramatically increasing upon awakening; however the morning surge in autonomic activity may be attributable to ambulatory and postural changes and warrants further investigation (Trinder et al. 2012). The decrease in BP is possibly due to sleep (Kerkhof et al. 1998; Van Dongen et al. 2001). The proportional increase in BP over the night, therefore, is likely not due to any intrinsic circadian rhythm of BP (cf. Trinder et al., 2001) but rather due to its correlation with the proportional increase of REMS over time, which does follow a robust circadian rhythm. During REMS, BP typically approximates quiet wakefulness (Trinder et al. 2012).

Autonomic activity varies considerably as a factor of sleep stage, such that during REMS, HR, HRV and BP can reach or exceed waking values (Trinder et al. 2001; Trinder et al. 2012). This is due to sympathetic dominance during this stage (Silvani and Dampney 2013). Stage N1 sleep appears to resemble quiet wakefulness as indexed by HF HRV (Bonnet and Arand 1997). Stage N2 is interestingly characterized by both relatively active and inactive cardiovascular function, when preceding transition to either REMS or N3 sleep, respectively, suggesting ultradian regulation of sleep (Brandenberger et al. 2005b). During stage N3 sleep, also termed slow-wave sleep for the defining characteristic of the stage, a sinusoidal signal oscillating slowly in the delta frequency (0.5 – 4.5 Hz) range (Achermann et al. 1993), vagal activity dominates .

For a variety of reasons, which shall be enumerated below, SWS is a potentially ideal state of consciousness for assessment of HRV (Brandenberger et al. 2005a). Slow-wave sleep characterized by physical quiescence, which reduces the probability of body movement-induced artifacts in the EEG or ECG signal considerably. Sympathetic nervous stimulation of muscle is decreased (Hornyak et al. 1991). In a recent study (Herzig et al. 2017b) of HRV recorded during SWS, no movement was detected at all in 89% of SWS stages investigated, and in the remaining 11%, minimal movement was detected, which lasted < 10 seconds per five minute SWS segment analyzed. Moreover, respiration

during SWS is steady and reflects RSA, which is predominantly mediated by the vagus nerves (Herzig et al. 2017b). Moreover, SWS is free of burst of sympathetic activity, such as tachycardia, which are present in REMS and are associated with phasic events (Trinder et al. 2012). Among elite athletes, HRV measurements made during 5 minutes of SWS compared to the first four hours of sleep and morning sleep showed the greatest correspondence to morning supine measurements after awakening, the current gold standard (Herzig et al. 2017b). Moreover, SWS is highly standardized, as sympathetic activity is lowest, BP variability is reduced, yet autonomic activity is constant and the individual is free of emotional stimuli (Herzig et al. 2018b). Fascinatingly, HRV itself can be used to identify SWS in the absence of the EEG (Herzig et al. 2018b; Herzig et al. 2017a; Herzig et al. 2017b). Thus, SWS presents itself as a highly standardized state that permits convenient and noninvasive HRV assessment.

The human heart is a tireless natural wonder and is of vital importance for life. This is reflected in its disorder and disease being associated with the leading cause of death and disability, particularly in industrialized nations. Essentially a pump, it delivers nutrient-rich blood to the trillion cells of the body and removes wastes. The heart has an intrinsic rate of contraction, which is coordinated by the specialized autorhythmic cells of the sinoatrial node. The Autonomic nervous system, which comprises sympathetic and parasympathetic components, impinges powerfully on heart function, in conjunction with other factors, such as baroreflex sensitivity and the renin-angiotensin system, among others, accelerating or decelerating heart rate. Heart rate can be used as a proxy for blood pressure dipping, and heart rate variability is an effective and noninvasive means of assessing autonomic regulation of the heart by means of statistics computed either in the time or frequency domain from RR intervals of the electrocardiogram. Heart rate variability is associated with psychological stress resilience, and those who reveal high vagal heart rate variability metrics tend to endorse greater stress resilience on questionnaires and are less likely to be diagnosed with a stressor or trauma-related disorder. Slow-wave sleep is a convenient window into vagal heart rate variability, which reflects a highly standardized state, free of confounds such as emotion, bursts of sympathetic activity or irregular breathing. Slow-wave sleep, thus, can be used to index healthy heart function in resilient individuals.

1.4 Wearable sleep trackers

For sleep researchers and clinicians, consumer-grade multi-sensor wearable sleep trackers represent a potentially economically viable, practical and convenient means of reliably and objectively recording activity levels and rest-activity behavior including sleep and may be more appropriate for ambulatory long-term longitudinal recordings compared to polysomnography (PSG) (de Zambotti et al. 2018;

Walch et al. 2019), although PSG perseveres as the gold standard in both clinical and research settings in the laboratory, whereas actigraphy is the prevailing US Food and Drug Administration (FDA) approved standard under ambulatory conditions (Hirshkowitz 2017). There is scant guidance as to the use of wearable sleep trackers in sleep research or sleep medicine, which has resulted in controversy and confusion with respect to appropriate application and validation (de Zambotti et al. 2019). This may, in part, be due to the dynamic nature of the wearable sleep tracker industry, which is introducing new devices constantly and (sometimes unceremoniously) updating its proprietary algorithms, and whereas the number of studies aiming to validate these devices is growing, the plodding pace of such published systematic scientific investigation is several steps behind the speedy pace of an industry whose devices both researchers and clinicians alike seek to marshal in the pursuit of knowledge and in the interest of benefiting public health (de Zambotti et al. 2019).

The obvious popularity of commercial fitness trackers is undeniable from even an anecdotal survey of trends and habits of the general public, and such an observation has been corroborated by statistical reports of sales of wearable devices, such as that of a current market leader Fitbit, whose sales have increased exponentially over the past decade (58,000 individual wearable units in 2010 vs. 15,988,000 in 2019) since founding of the company, as well as by revenue, whereby Fitbit has reported a full year revenue of $1.5 billion in 2018 (Fitbit Inc 2019), representing a sizeable scaling up in profits from the mere $5 million earned by that same company in 2010; although sales may now be beginning to decline (Statista 2020).

Historically, the predecessor in many respects to both first- and second-generation wearable sleep trackers was wrist-derived activity monitoring, which was conducted with dedicated instruments typically resembling a wristwatch and were implemented with near exclusivity by specialists, primarily in medical or research settings (Walch et al. 2019). Such actigraphy devices, as they are referred to, are approved by the FDA to measure movement and estimate sleep and are the accepted and primary alternative to PSG under ambulatory conditions (de Zambotti et al. 2019). Actigraphy devices consist of a three-axis accelerometer and in some instances are also equipped with an embedded light sensor for use in longitudinal estimation of behavioral variables of interest to the investigator in an ambulatory setting, e.g., sleep habits, bedrest and rise times, light exposure, etc. (Ancoli-Israel et al. 2003; de Zambotti et al. 2018; Scott et al. 2020; Smith et al. 2018; Walch et al. 2019) (**Figure 1.3)**. The basic assumption in actigraphy is that motion implies wakefulness, whereas no motion implies sleep (de Zambotti et al. 2019). Use of actigraphy typically involves at least two in-person visits for setup and data readout with a sleep specialist, however, and the devices themselves and associated software and device readers are and costly (ca. $1,000 per unit) compared to consumer grade wearable devices (ca. $100 per unit), such as wearable sleep trackers (de Zambotti et al. 2019; Douglas-Walton 2020; Walch et al. 2019). By comparison, consumer grade wearable sleep trackers

are sleek, come in a variety of styles, colors and physical or ergonomic accessory categories (e.g., fashionable jewelry, headbands, wristbands, armbands, sensor clips, etc.) and offer attractive and easy to navigate graphic user interfaces, cloud-based platforms for data storage accessible via Internet connection and intuitive data visualization, all at one's fingertips, not to mention an array of other functions of probable interest to the consumer, such as timekeeping, Internet access or telephone functions, among many others (de Zambotti et al. 2019; Douglas-Walton 2020).

There has been a growing proliferation recently of such commercially available devices which are commonly marketed as fitness trackers (e.g., Fitbit, Apple, Garmin, among others) toward consumers and non-health specialists, any of which may utilize multiple sensors to capture a variety of biosignals (activity, pulse, skin conductance, temperature) to estimate a physiological endpoint of interest, e.g., sleep macrostructure (de Zambotti et al. 2019; de Zambotti et al. 2018; Douglas-Walton 2020; Reimer et al. 2017; Walch et al. 2019). These devices, which inform the wearer only of "general wellness" (p. 1538), are not regulated by the FDA, although emerging regulatory models, such as the Digital Health Software Precertification program, may impact prevailing legal and market conditions of wearable devices sooner or later (de Zambotti et al. 2019).

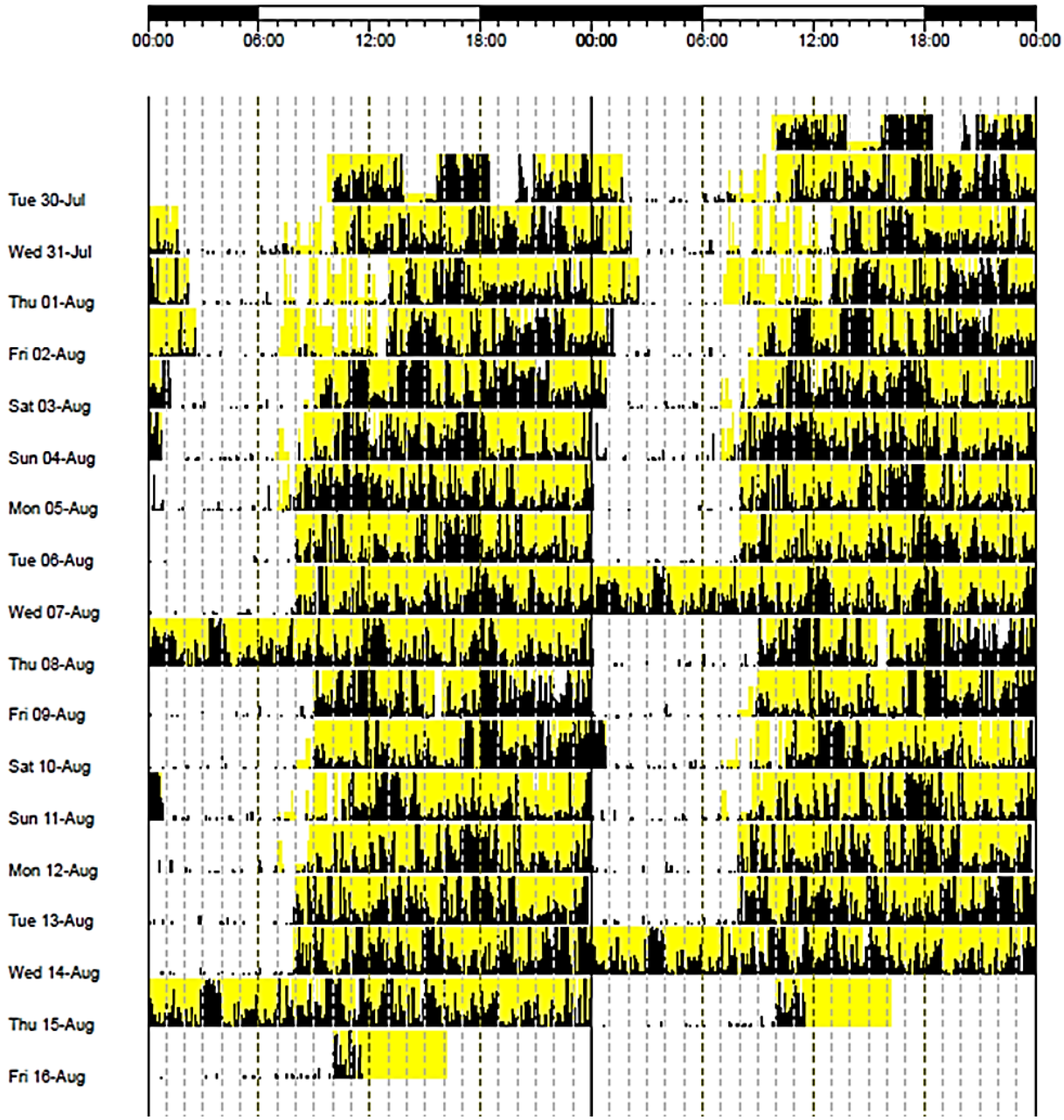

Figure 1.3 Double raster plot 'actogram' of activity (black) and light (yellow) data output captured by a conventional actigraphy device. Experimentally imposed periods of sleep deprivation can be observed on the nights of Wed 07-Aug and Wed 14-August. Horizontal axis shows clock time and day/night or light/dark episodes (black vs. white bars); vertical axis shows day of the week and date.

De Zambotti and coworkers (2019) have offered the definition of "wearable sleep trackers" in particular as "over-the-counter, relatively low-cost devices available without a prescription or clinical recommendations" (p. 1538). Such devices claim to be able to calculate sleep parameters and do so in many cases with proprietary algorithms of increasing sophistication, which perform such calculations automatically (Reimer et al. 2017) and in some instances mathematically incorporate functions derived from *a priori* knowledge of the biological mechanisms strongly impacting sleep – wake

behavior (Walch et al. 2019), i.e., the sleep homeostat and evoked circadian rhythm as characterized by the two-process model of sleep regulation (Borbély 1982). Whereas the algorithms in conventional actigraphy devices were disclosed by the manufacturer (e.g., Philips Respironics, Inc. Bend, OR) or were publicly available (e.g., Cole-Kripke and Sadeh algorithms) (de Zambotti et al. 2019), those algorithms in consumer grade wearable devices are proprietary and remain mostly undisclosed (Walch et al. 2019), nor is raw data typically made available (de Zambotti et al. 2019). Furthermore, by comparison to what is known about the algorithms of contemporary wearable sleep trackers, the algorithms of actrigraphy devices are of lower complexity (de Zambotti et al. 2019). As de Zambotti and colleagues (2019) remind, although most studies comparing actigraphy to PSG report high sensitivity (detection of true sleep) and accuracy (general performance in discerning true waking and sleep), actigraphy is intrinsically hampered in the detection of true waking (specificity) as waking unaccompanied by motion goes undetected.

Despite the temptation to use wearable sleep trackers by members of the scientific and medical community and profit from the "digital health revolution" (p. 1538) (de Zambotti et al. 2019), validation of many of these instruments against PSG is still generally lacking, which nevertheless does not always appear sufficient enough of a deterrent for investigators to look elsewhere for conventional instruments that are already reliable, accurate and validated (e.g., actigraphy, PSG) (de Zambotti et al. 2019). What further confounds validation efforts are updates to firmware or software, which may be changed without notice (de Zambotti et al. 2019), with the attendant consequence being that even if one generation of a device were to be successfully validated against PSG, a subsequent update may have voided such validation efforts and possibly without the awareness of investigators of the update having taken place. Perhaps of even greater hazard to investigators conducting longitudinal studies over prolonged periods of time, however, is the risk that an update, silent or formally disclosed, may occur at any point throughout data collection and potentially seriously jeopardize study outcomes (de Zambotti et al. 2019). Moreover, access to data is in some instances (e.g., Fitbit) indirect and facilitated exclusively by the vendor with the vendor's involvement and consent on a case-by-case basis, such that data must be queried from external repositories after it has already been gathered by the device, preventing direct access to raw data and introducing a sometimes burdensome intermediate step in the data extraction process for investigators.

These obstacles may temper enthusiasm for the implementation of these devices in research or clinical undertakings (Walch et al. 2019). Additionally, there is no prevailing consensus as to how the mushrooming popularity of wearable sleep trackers should most appropriately be capitalized upon by sleep clinicians and researchers with respect to standards or implementation, as no widespread agreement on these points among specialists can be discerned (de Zambotti et al. 2019). Furthermore, there is presently, in the words of one group (de Zambotti et al. 2019) keenly monitoring the

development of wearable devices in sleep science, an “alarmingly” (p. 1539) scarce amount of knowledge or understanding regarding the performance of such devices given the exponential growth in the field of sleep science. It is critical to recognize that consumer grade wearable sleep trackers are not specifically developed for clinical or research purposes but rather are meant for leisure and novelty purposes of the general public (de Zambotti et al. 2019).

Nevertheless, consumer grade wearable sleep trackers have not gone unnoticed or unappreciated by chronobiologists, sleep scientists and sleep clinicians, and there is an emerging literature on various aspects of such devices with respect to how well these devices can measure rest-activity behavior and sleep compared to PSG (de Zambotti et al. 2019; Haghayegh et al. 2019b; Roberts et al. 2020; Scott et al. 2020), despite the aforementioned caveat of validation challenges. Initial results are even promising with respect to detecting sleep onset (Scott et al. 2020), sleep quality (Roberts et al. 2020) sleep stages (Walch et al. 2019) and sleep-wake behavior (Riedy et al. 2020) compared to PSG. De Zambotti and colleagues (2019) identify the exponentially swelling popularity of these devices among scientists and cite the nearly 700 abstracts and articles in peer reviewed journals just for Fitbit alone.

Polysomnography utilizes electrophysiological signals to measure sleep. It does so by harnessing the output of postsynaptic potentials of millions of neurons in the cerebral cortex via electroencephalography (Nestler et al. 2009) by means of electrodes affixed to the scalp (AASM 2007). An amplified signal of this derived cortical activity is recorded simultaneously with electromyographic signals obtained conventionally from electrodes placed on or beneath the chin (or both), electrooculgraphic signals derived from electrodes placed bilaterally at the supraorbital and infraortbital ridges, 1 cm away from the respective outer canthus, and electrocardiographic signals from leads placed on the torso (modified lead II configuration) to visually discern sleep macro- (e.g., stages, cycles, etc.) and microstructure (e.g., arousals, spindles, K-complexes, other wave forms of varying description, etc.). In some research settings and routinely in clinical practice, respirometry utilizing respiratory inductance plethysmography facilitated by thoracic and abdominal belts is conducted; snore microphones, pulse oximetry and electromyography of the legs to detect restless leg syndrome and other sleep disorders are also typical (AASM 2007). Variables of sleep quality and quantity (e.g., sleep latency, sleep duration, sleep efficiency, waking after sleep onset, among many others) and sleep timing can be derived from the data obtained from these instruments. More sophisticated analyses can be conducted on these data as well, such as power spectra analysis. The richness, diversity and resolution of physiological data captured by PSG, the reproducibility and validity of such data, in addition to the internationally standardized methods of PSG application, e.g., the International 10-20 System of Jasper (1958), and data interpretation technique (AASM 2007), render PSG the longstanding and widely accepted gold standard for assessing sleep in both research

and clinical scenarios (Hirshkowitz 2017). Despite its inherent strengths, PSG is simply too costly and cumbersome to be applied to measurements for prolonged periods of time outside research projects. Moreover, PSG is typically confined to a sleep laboratory and requires specialized equipment, most prominently a dedicated PSG apparatus, in addition to the expertise of professionally trained sleep personnel for application of PSG instruments, monitoring of recordings, scoring and finally interpretation of PSG data (de Zambotti et al. 2019).

As can be reasonably expected, this makes a the relatively inexpensive, flexible and longitudinally viable alternative of wearable sleep trackers, which can be implemented in both laboratory and ambulatory settings, an enticing option indeed for the sleep scientist or clinician; however, the challenge of competing with the performance of a measurement system as comprehensive as PSG by a single device worn on one wrist (or elsewhere: ring finger, e.g., Oura Smart Ring) is formidable indeed. Nevertheless, the number of devices which test their mettle against PSG is increasing (Douglas-Walton 2020), as is their performance and the number of citations of scientific investigators utilizing them (de Zambotti et al. 2019), although none have (yet) reached a level of performance, such that a substitute for PSG could be considered (Danzig et al. 2020; Haghayegh et al. 2019b). De Zambotti and colleagues (2019) distinguish between first and second generation wearable sleep trackers, the key distinguishing feature being that whereas first generation devices relied on motion alone to track sleep, resulting in the misclassification of periods of quiet wake as sleep, the second generation of multisensory devices utilize an array of biosignals, which should theoretically overcome the limitations of first generation devices. Devices which capitalize on well-characterized salient autonomic changes accompanying sleep dynamics (Cajochen et al. 1994; Carrington et al. 2005; Trinder et al. 2001; Trinder et al. 2012) by using photoplethysmographic (i.e., optical sensor-aided measurement of blood volume changes) assessment of heart rate and heart rate variability, for instance, stand a much better chance at accurately identifying sleep macrostructure than conventional motion-only models, at least in healthy samples (de Zambotti et al. 2019). Indeed, variability in population health (e.g., normal health vs. afflicted with a sleep disorder), age (e.g., children vs. adults) and recording environment (e.g., sleep laboratory vs. naturalistic setting) can significantly impact performance, and because most validation studies were conducted in the laboratory under controlled conditions, performance of wearable sleep trackers compared to PSG beyond this setting remains largely an unanswered question (de Zambotti et al. 2019).

Due to data storage restrictions of historical actigraphy devices, data was most commonly recorded at a resolution of 1 minute activity counts; contemporary wearable sleep trackers, however, can in some instances yield such a resolution or higher and during sleep a data granularity fine enough to yield 30 second epochs of sleep (conforming to the prevailing convention of sleep stage duration in PSG) and states familiar to researchers and clinicians, i.e., deep (N3), light (N1 + N2) and rapid eye

movement (REM) sleep, facilitating in some cases epoch-by-epoch comparison between device output and that of PSG (de Zambotti et al. 2019). This gets at the ultimate contrasting feature which separates second-generation wearable sleep trackers from actigraphy and even from their first-generation consumer-grade predecessors: the ability to not only discern sleep from waking in a simple yes-no dichotomous fashion, but to zoom in on the finer granularity of sleep macrostructure and characterize the distinct profile of a sleep episode as it progresses from stage-to-stage and cycle-to-cycle (de Zambotti et al. 2019).

The majority of validation studies (de Zambotti et al. 2019; Liang and Alberto Chapa Martell 2018) are in actuality "second-step validations" (p.1544), meaning that signals, which are to be validated, have already been processed before any comparison can be made, leaving only comparison of post-processed signals, with few exceptions (Walch et al. 2019), and no access to raw data due to the "black box" (p. 1544) nature of these instruments (de Zambotti et al. 2019). In addition, there are is no prevailing convention or any guidelines in exactly how devices should be validated or how their performance should be interpreted (de Zambotti et al. 2019).

Performance of first-generation wearable sleep trackers typically fared comparably to that of actigraphy, such that on average, sensitivity was high (90%) in classifying sleep but specificity (classifying waking) was low, which is reflected in inflated estimates of total sleep time and underestimates of waking after sleep onset compared to PSG (de Zambotti et al. 2019). Second-generation devices typically reveal high (60-75%) performance accuracy in classifying light (N1 + N2) and REM sleep but lower performance accuracy in detecting deep (N3) and REM sleep (de Zambotti et al. 2019). Sleep latency represents a particularly challenging variable for wearable sleep trackers to determine with precision, and this is reflected by high standard deviations (ca. 40 minutes) in this variable in one study in adolescents (Pesonen and Kuula 2018) using the Polar A370, although sleep onset and latency did not differ significantly compared to PSG in that report (de Zambotti et al. 2019). Variability is due largely to relying on indirect estimation of lights out, which is performed by an algorithm, whereas in the sleep laboratory with PSG, lights out is typically determined by the experimenter, who is most often the one turning off the lights, or is captured online by an event marker, although it should be mentioned that off-line retroactive correction of lights out can be performed to adjust sleep parameters by users in some device types (de Zambotti et al. 2019). In a report evaluating the performance of the Fitbit Charge 2 against ambulatory single channel PSG (Liang and Alberto Chapa Martell 2018), a positive delay of up to 20 minutes was more often than not observed (ca. 70%), whereas in nearly one quarter of cases the delay exceeded 20 minutes (de Zambotti et al. 2019). One report (de Zambotti et al. 2017) compared Fitbit Charge 2 against PSG in normal healthy individuals (n = 35) as well as in a subsample of individuals with periodic limb movement disorder (PLMD) (n = 9) of both sexes in the laboratory. Among normal sleepers, 96%

sensitivity (accuracy in classification of sleep), 61% specificity (classifying waking), 81% accuracy in classifying light sleep (N1 + N2 sleep), 50% in classifying deep (N3 sleep) and 75% accuracy in classifying REM sleep was reported (de Zambotti et al. 2017). In this study, PSG total sleep time was significantly overestimated (ca. 10 minutes), as was light sleep (ca. 30 minutes), whereas deep sleep was underestimated (ca. 20 minutes). Duration of REM sleep and waking after sleep onset did not differ significantly between Fitbit and PSG in that report. Sleep onset latency was underestimated by 4 minutes. With respect to sleep cycles, 82% of non-REM-REM sleep cycles were correctly identified by Fitbit compared to PSG. Performance of the device in reference to PSG in the subsample of PLMD was comparable that in the main group, but no direct statistical comparison was made due to the low sample sizes of these respective groups. With regards to validation indices, only two individuals exceeded Bland-Altmann agreement limits for all sleep measures compared. The performance of the Fitbit Charge 2 reported in this study is better than the average second-generation wearable sleep tracker regarding accuracy in classifying light (N1 + N2) and REM sleep but falls within the range of performance of second-generation wearable sleep trackers for other parameters, i.e., (60-75%) performance accuracy in classifying light and REM sleep but lower performance accuracy in detecting deep (N3) and REM sleep (de Zambotti et al. 2019).

In summary, consumer-grade multi-sensor wearable sleep trackers are profitable and very popular among consumers. They represent an attractive and in many respects practical alternative to both gold standard ambulatory PSG and actigraphy, but are associated with appreciable caveats and limitations for the sleep scientist or clinician. Most notably among the concerns voiced by scientists closely monitoring the development of consumer-grade wearable sleep trackers and their use in scientific investigations is the absence of any consensus among scientists on how these devices should be implemented and validated as well as oversight by a state regulatory body, which could establish standards in conjunction with scientists for standardization of use or validation procedures. These devices were conscientiously designed and marketed toward the sports leisure market in for-profit ventures and were never intended for use as research instruments. Any benefit drawn by scientists is, thus, purely coincidental. Their construction and computer algorithms with which health and sleep parameters are calculated are intellectual property, kept by developers as strict trade secrets, as is any raw data gathered, foiling any true primary-validation attempts. Updates to firm- or software can, moreover, occur at any moment and represent a not inconsiderable hazard for those collecting data with these devices over long periods of time. An update could, furthermore, render any successful and already published validation attempt obsolete and, worse, inaccurate, which may lead to false conclusions being drawn, misinformed research decisions made and wasted investments going forward in research and medicine. The speed of serious systematic research is simply outpaced by the wearable sleep tracker industry, and more devices are released each year than can be reasonable

validated. Despite these limitations, however, the performance of wearable sleep trackers in estimating conventional sleep parameters compared to PSG is very promising indeed and is at least as good and if not better than conventional actigraphy, and should cause for both researchers and clinicians to be optimistic about the prospect of these trackers ultimately being of benefit to science and public health and not a hindrance. Whereas no prevailing consensus can be cited with respect to the validation and use of such devices presently, there are established procedures (simultaneous comparison with PSG, within-subject analysis, regression, epoch-by-epoch analysis, error matrixes, Bland-Altmann plots, etc.), which could be standardized, and these topics are being actively discussed by an increasing number of specialists in the field and there is evidence that the industry may also be listening (de Zambotti et al. 2019).

1.5 Study design

Data for this dissertation was collected between July 21, 2017 and November 2, 2018 within the framework of a Clinical Research Priority Program (CRPP) "Sleep and Health" and represents a collaboration between the Department of Psychology and the Institute of Pharmacology and Toxicology of the University of Zurich. This project was made possible by the generous cooperation of Schutz & Rettung Zurich, Rettungsdienst Winterthur and Stadtpolizei Winterthur, who provided the study participants, aided in recruitment and made vital infrastructure available to project staff. The study design and methods of data collection will be described in this chapter. This project (2016-01357) was approved by the Cantonal Ethics Commission Zurich, Switzerland. All participants provided written informed consent prior to participating in the study.

Participants were screened for eligibility by study staff and a urinary drug screening (Drug-Screen Multi 12-AE, Nal von Minden GmbH, Regensburg, DE) was conducted. Exclusion criteria consisted of > 5 alcoholic drinks / week, diagnosis of neurological disorder and consumption of illicit drugs. Inclusion criteria consisted of employment at Schutz & Rettung Zurich, Rettungsdienst Winterthur and Stadtpolizei Winterthur. This naturalistic study consisted of 4 data collection appointments spanning 7 months. At appointment 1 (T0), participants provided biological specimens for genotyping and protein assay and completed a questionnaire battery administered by the Unipark web page on a personal computer including among others the Horne-Östberg Morningness-Eveningness Questionnaire – A Reduced Scale, Pittsburg Sleep Quality Index (PSQI), Perceived Stress Scale-10 (PSS-10), demographic and health data questionnaires and Post-Traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (PCL-5). Health and demographic data were collected and the Clinician-Administered PTSD Scale for DSM 5 (CAPS-5) was administered by native German-speaking study staff members. Participants were

provided with a commercially-available activity and heart rate monitor (Fitbit Charge 2™, Fitbit Inc., San Francisco, CA, USA). In addition, a link to the first in a series of 9 internet web page-based study-specific post-traumatic stress and sleep quality questionnaires administered via Redcap was created on their smart phone display. Briefly, participants were instructed to open the Redcap web page via the link should they have experienced a potentially traumatic event and then answer questions pertinent to this event. Once the first questionnaire (Post Stress Report) was successfully completed, a second questionnaire (Detailed Stress Report) was automatically triggered, which resulted in a link being sent via SMS to the participant's smart phone 60 minutes later. This second questionnaire contained further questions to the event and requested that participants elaborate on their experience and the specific details of the event. Upon successful completion of this second questionnaire, the transmission of the first in a series of 7 sleep questionnaires was triggered. Links to the sleep questionnaires were sent each morning over the subsequent 7 days via SMS. These questionnaires asked participants to provide information about their sleep quality, memories of the potentially stressful event and strategies of managing perceived stress relating to the event. Each subsequent morning, an SMS would be sent to the participant's smart phone containing a link to the sleep questionnaire. Successful completion of each sleep questionnaire would trigger the dissemination of the next, until all 7 sleep questionnaires were successfully completed, at which point the participant would be informed that this was the final questionnaire and thanked. Data from all 9 of the Redcap questionnaires were saved online automatically. Participants then began the principal data collection segment of the study. This segment comprised a month of continuous data collection via Fitbit Charge 2™ and Redcap, in the event a potentially stressful event was experienced. Redcap data are not reported in this thesis.

Participants met again with study staff upon completion of the scheduled one month of continuous data collection at appointment 2 (T1). Participants returned their Fitbit Charge 2™ and completed a second Unipark questionnaire battery. A second saliva sample was provided by participants. Participants were debriefed and then received payment of CHF 50 – CHF 150. The specific amount of payment was contingent on degree of participation, such that participants would receive CHF 50 if they successfully completed the 1 month of continuous data collection. If participants, however, had opted for the three nights of polysomnography (PSG), then they received an additional CHF 100.

Polysomnographic recordings were made with a portable PSG system (SOMNOscreenTM Plus, SOMNOmedics GmbH, Randersacker, DE) of night sleep in the participant's home or dedicated sleeping quarters of their workplace in a subset of 61 participants, who explicitly volunteered for this optional part of the study. Typically, study staff visited participants at their place of residence, where scalp electrodes (Fz, Cz, Pz, Oz, C3, C4, A1, A2) were applied according to the International 10-20

System and LOC, ROC, EMG, ECG, GND electrodes according to AASM standards. Questionnaires addressing caffeine, alcohol consumption, naps and medications that day were administered. The Positive and Negative Affect States (PANAS) and Karolinska Sleepiness Scale (KSS) were also completed. Questionnaires on bedtime and wakeup time, perceived sleep latency, nighttime awakenings and a second PANAS and KSS were completed in the morning. Two consecutive nights of polysomnography were recorded per participant, which consisted of an initial adaptation night followed by a baseline night. Baseline nights always occurred directly after adaptation nights. A post-potentially traumatic event night recording was planned and would be conducted spontaneously in the event a participant in this subset reported a potentially-traumatic event to study staff. Such sleep recordings could only be completed in a small number of participants (n = 2) due to the general absence of reported potentially traumatic events within this subsample during day shifts. Participants were shift workers, but only night sleep after a day shift was recorded to minimize the influence of factors related to potential circadian misalignment which accompany daytime sleep in shift work scenarios.

Two further data collection appointments (appointments 3 and 4) occurred 3 months and 6 months after completion of the study month, respectively. These data collection appointments consisted of the completion of questionnaire batteries and the CAPS interview. Upon successful completion of appointment 4, participants received a "sleep feedback" report, which contained information derived from sleep data analyzed from the Fitbit Charge 2™ and sleep electroencephalogram showing variables related to sleep stages, sleep quality and sleep timing over the study month.

1.6 Aims of the current thesis

The aims of this thesis were to characterize the rest-activity behavior of a sample of emergency medical rescue workers and law enforcement officers performing shift work under naturalistic conditions with a commercially available wearable device (Fitbit Charge2™) and ascertain to what extent the demands of their professions including shift work interfere with their abilities to achieve sleep of sufficient quantity and quality. These variables were operationalized with the conventional variables of sleep duration, wake after sleep onset (WASO), REM sleep latency, and REM sleep percentage. Variance in the preferential management of sleep episodes and their duration across a 24-hour period for each individual over the one month study period was also investigated. A variety of demographic, health and lifestyle variables were surveyed in this sample and a selection of these variables was used as covariates in analyses related to sleep and cardiovascular endpoints to determine to what extent observed inter-individual variability may be due to differences in, for

example, sex, age and varying rates of caffeine and alcohol consumption as well as physical fitness. Please see chapter 2, manuscript 1, for a detailed report.

An attendant aim was to capture the profile of selected cardiac-autonomic endpoints (mean and variance of HR) during sleep and waking. An emphasis was placed on the development of these variables within individual sleep stages (NREM "light" sleep, NREM "deep" sleep and REM sleep) as constituents of the first four NREM-REM sleep cycles of the night. Considerable ultradian variability in both sleep structure and autonomic regulation is a salient feature of the sleep PSG and ECG, respectively. Under normal conditions, autonomic regulation of the cardiovascular system varies within a given sleep state as well as in the transition from one state to another in a predictable fashion, whereby ECG changes precede PSG indications of sleep state change by several minutes (i.e., rapid ECG HR acceleration preceding PSG REM sleep and ECG HR deceleration preceding PSG NREM sleep). A global trend of gradually decreasing heart rate is observed for the entire sleep episode, and the evoked circadian rhythm has been well established in both selected sleep (e.g., REM sleep) and cardiovascular (e.g., HR) endpoints. We sought to investigate the extent to which this pattern persists under naturalistic conditions in a shift work scenario and at varying times of day in our sample and to establish a link to the highly prevalent phenomenon of circadian misalignment, which frequently accompanies shift work.

In the interest of elucidating further inter-individual differences in preferential management of rest-activity behavior, we stratified individuals in our sample by score on the highly validated and widely used Horne-Östberg Morningness-Eveneningness Questionnaire – A Reduced Scale (rMEQ), which assesses a trait-like behavior influencing the preferential timing of a variety of behavioral cycles, such as sleep/wake and fasting/feeding, and is putatively driven, at least in part, by variance in genetic substrates, which underlie circadian and homeostatic characteristics, as well as by age and other environmental or psychological factors. In a data-driven approach, we created two groups of individuals in our sample, corresponding to the strongly bi-modal distribution of rMEQ scores and compared these groups with respect to the distribution of variables of sleep quality and cardiac-autonomic function. We could show that Preferential Evening Types compared to Preferential Morning Types seem to cope differently with the demands of shift work, such that sleep of greater duration, which was more distributed across a given 24-hour period. The mean HR was higher in this group compared to the Preferential Morning Types. These findings are explored in more detail in chapters 3 and 4, manuscripts 2 and 3, respectively.

In the interest of demonstrating the integrity and validity of our Fitbit-derived findings, we conducted a validation study comparing Fitbit-derived variables of sleep quality and structure to counterparts derived from the gold standard of PSG, explored in Chapter 2, manuscript 1. This validation study demonstrates that Fitbit captures these variables with an accuracy and reliability that

is at least sufficient to detect significant and robust differences in rest-activity behavior and cardiovascular regulation.

Validation of Fitbit Charge 2™ sleep and heart rate estimates against polysomnography in shift workers at home

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Abstract

Multi-sensor fitness trackers offer the perspective to longitudinally estimate sleep quality in a home environment that can outperform traditional actigraphy. To benefit from these new tools to objectively assess sleep for clinical and research purposes, multi-sensor wearable devices require careful validation against the gold standard of sleep polysomnography (PSG). Naturalistic studies in samples drawn from clinical populations favor validation. With this purpose in mind, we conducted a validation study of Fitbit Charge 2™ against portable home PSG in a shift-work population composed of 59 first-responder police officers and paramedics. Reliable comparison between the two measurements was ensured through data-driven alignment of the time series recorded in each night. Epoch-by-epoch analyses (EBE), together with Bland-Altman plots were used to assess sensitivity, specificity, accuracy, matthews correlation coefficient, bias and limits of agreement. Sleep onset and offset, total sleep time, and the durations of rapid-eye-movement (REM) and non-rapid-eye-movement (NREM; N1 + N2 and N3) sleep stages displayed unbiased estimates, yet with non-negligible limits of agreement. By contrast, the proprietary Fitbit algorithm overestimated REM sleep latency by 29.4 min and wake time after sleep onset (WASO) by 37.1 min. EBE analyses indicated better specificity than sensitivity, with a higher accuracy for WASO (0.82) and REM sleep (0.86) than for N1 + N2 (0.55) and N3 (0.78) sleep. Fitbit heart rate (HR) displayed a small underestimation of 0.9 beats-per-minute (bpm) with a limited capability to capture sudden HR changes because of the reduced time resolution when compared to PSG. The underestimation was smaller in N2, N3, and REM sleep stages (0.6-0.7 bpm) compared to N1 sleep (1.2 bpm) and wake (1.9 bpm), indicating a state-specific bias. Finally, Fitbit suggested a distribution of all sleep episode durations that was different to that derived from PSG and showed non-biological discontinuities, indicating potential limitations of the staging algorithm.

Keywords: wearables, actigraphy, polysomnography, validation, multisensory

Introduction

Sleep is not an invariant state, but is highly diverse, nuanced, and transient, with no absolute or dichotomous starting or ending point. This fact accentuates the necessity of utilizing highly sensitive and precise instruments for its accurate measurement in healthy and clinical populations. Polysomnography (PSG) is the prevailing gold standard in clinical and research settings (Hirshkowitz 2017). A PSG measurement utilizes electrodes and sensors placed on the body according to international standard criteria to detect electrical signals reflecting underlying physiological processes (Hirshkowitz 2015) An all-night PSG recording yields a vast amount of data at high temporal resolution. From a single PSG recording, it is possible to capture sleep macrostructure (e.g., stages, cycles), microstructure (e.g., K-complexes, spindles, arousals), compute the power spectra density of desired frequency bins, as well as heart rate (HR) variability, among many other variables. From these quantitative data it is possible to calculate variables of sleep quality, such as sleep onset latency and sleep efficiency, and make prognostic statements about the health of an individual. Despite the inherent advantages of PSG, there are attendant disadvantages, such as high cost, need for personnel trained in technical aspects as well as in interpretation of data, and the device itself, which is typically practical only in a static setting, usually necessitating a dedicated sleep laboratory, although ambulatory systems do exist (de Zambotti et al. 2017). With these considerations in mind, it is clear that an inexpensive, practical, and portable alternative that is equally accurate and reliable in measuring sleep would be very welcome for clinicians and scientists alike.

The currently only validated and United States Food and Drug Administration (FDA) approved alternative to PSG in ambulatory settings is actigraphy (de Zambotti et al. 2019). Actigraphy describes a measurement of movement by means of a multi-axis accelerometer in a device resembling a wristwatch, sometimes accompanied by an embedded light sensor. Actigraphy prospectively captures rest-activity behavior in an individual, such as sleep habits, bedrest, rise times and light exposure (Ancoli-Israel et al. 2003; Borbély et al. 2017). The basic assumption of actigraphy is that motion implies wakefulness, whereas no motion implies sleep. Fully-disclosed Sadeh (Sadeh et al. 1989) and Cole-Kripke (Cole et al. 1992) algorithms are used to compute sleep variables with some precision, but performance varies compared to PSG due to the inherent limitation of actigraphy in discriminating sleep from waking that is not accompanied by movement (de Zambotti et al. 2019; de Zambotti et al. 2017). Actigraphy represents a dedicated scientific instrument used almost exclusively in clinical and research contexts and depends on specialists for setting up and interpretation of data (Walch et al. 2019).

Recently, there has been greater acceptance but also controversy among the scientific community in utilizing commercially available wearable devices, termed fitness trackers, in research (Inderkum and Tarokh 2018). Fitness trackers are multi-sensor consumer grade devices and represent

a cost-efficient, practical and convenient means of objectively collecting rest-activity data longitudinally under ambulatory conditions (de Zambotti et al. 2019). Fitbit is a market leader (Statista 2020), and there have been efforts to validate its devices, such as the Charge 2™, against PSG (de Zambotti et al. 2019; Scott et al. 2020) and the portable single channel EEG Sleep Scope device (Liang and Alberto Chapa Martell 2018). One advantage of such devices is the measurement of HR via photoplethysmography (PPG). It is known that changes in the activity of the autonomic nervous system are coupled to changes in electroencephalographic (EEG) brain wave patterns (Cajochen et al. 1994; Trinder et al. 2012). In particular, various HR measures are correlated with the different sleep states (Ako et al. 2003). This potentially permits a fitness tracker, such as Fitbit Charge 2™, to estimate an array of sleep variables with a proprietary algorithm above and beyond that of conventional actigraphy (Fitbit Inc. 2020b; Karlen and Floreano 2011; Karlen et al. 2008).

One study found that on average Fitbit Charge 2™ moderately underestimated HR of 5.9 bpm compared to electrocardiogram (ECG), whereas precision can be poor for individual measurements as reflected by wide limits of agreement (LoA) (Benedetto et al. 2018).To obtain a second-to-second HR resolution, those authors recorded the HR data displayed live in the Fitbit app with a camera. Another study in 35 healthy individuals used 5-min HR averages provided by Fitbit and compared them to electrocardiogram (ECG) derived HR measures (Haghayegh et al. 2019a). These researchers found that Fitbit Charge 2™ tended to slightly overestimate HR in ranges < 50 bpm (bias = 0.51 bpm) and to underestimate HR in ranges > 80 bpm (bias of 0.63 bpm). The predecessor model Fitbit Charge HR™ displayed an underestimation of HR in the same range of 0.88 bpm (de Zambotti et al. 2016). Performance of the Fitbit Charge 2™ for various sleep variables was shown in one recent laboratory study to be good (de Zambotti et al. 2017). The device displayed a 9-min overestimation of total sleep time (TST), consisting of sleep offset (S_{off}) - sleep onset (S_{on}). These authors also found that Fitbit's "light" sleep stage, interpreted to be comparable to N1 + N2 sleep stages, was overestimated by 34 min, whereas sleep onset latency was underestimated by 4 min and Fitbit's "deep" sleep stage, assumed to be equivalent to N3 sleep, by 24 min compared to PSG referents in a group of healthy adults (n = 35). No bias was observed for wake after sleep onset (WASO) or duration of rapid eye movement (REM) sleep (REM_d). Findings for individuals (n = 9) with periodic limb movements of sleep (PLMS) were comparable (de Zambotti et al. 2017). Another recent study in 65 individuals with symptoms of obstructive sleep apnea (OSA) contradicted the above mentioned unbiasedness of WASO for two Fitbit devices, Fitbit Charge 2™ and Fitbit Alta HR ™, such that both devices underestimated WASO, possibly indicating variable performance as a function of the clinical population investigated (Moreno-Pino et al. 2019). In a study of 25 healthy young adults (Liang and Alberto Chapa Martell 2018), Fitbit Charge 2™ derived sleep variables were compared to a portable single-channel clinical EEG sleep monitor called Sleep Scope, which shows 86.9% agreement with

PSG (Liang and Alberto Chapa Martell 2018). This validation study was conducted at the participants' homes and found TST to be underestimated by 12.3 min, "light" sleep by 42.4 min and REM sleep by 11.6 min. An overestimation was observed for WASO with 24.5 min and deep sleep with 39.8 min. It should be noted that these estimates showed large standard deviations.

The rather inconsistent sleep findings reported in previous validation studies (de Zambotti et al. 2019) comparing Fitbit Charge 2™ with PSG hinder comparability and imply that further research is warranted. In addition, it is necessary to validate consumer-grade wearable devices under naturalistic conditions in diverse and at-risk populations, since it has been shown that such factors may impact performance. To our knowledge, no study yet attempted to validate Fitbit Charge 2™ against PSG in populations with atypical health status or health risk status and in naturalistic or ambulatory PSG environments, for example, in emergency medical rescue workers and law enforcement personnel studied at home. These populations regularly perform shift work and exhibit an elevated risk to develop cardiovascular and metabolic disorders (Kecklund and Axelsson 2016; Knutsson 2003), are exposed routinely to danger and potentially traumatic events and hence are at greater risk for trauma and stressor-related disorders (Berger et al. 2012). The development of such adverse health outcomes due to the nature of their occupation may be attenuated by high-quality sleep. Thus, we sought to validate the usefulness of Fitbit Charge 2™ to evaluate sleep quality in first responder shift workers under naturalistic conditions with a special focus on rigorous data preprocessing and time alignment of data recording.

Methods

Study sample

The participants of this study were recruited by various informational media, email, and presentations at shift change as part of a larger study investigating sleep and resilience to psychological stress and trauma from July 2017 through November 2019. They completed one month of monitoring of wrist derived rest-activity behavior with a Fitbit Charge 2™ (Fitbit Inc., San Francisco, CA, USA) that was worn continuously by all individuals on their non-dominant wrist.

The Ethics Commission of the Canton of Zurich approved (2016-01357) all study protocols and experimental procedures, and written informed consent was obtained prior to participation. Participants invited to participate fulfilled all inclusion criteria of age between 18 - 65 years, body mass index (BMI) $\leq$ 26 (or if exceeding a BMI of 26, typical of very athletic participants, an absence of sleep problems, e.g., sleep breathing disorders, was reported), current employment in one of two participating emergency rescue stations and one police station in the greater Zurich area of Switzerland, possession of a smart phone, and German language fluency. Exclusion criteria comprised the presence of a neurological disorder diagnosis or head injury with potential to affect EEG

variables, reported intake of > 5 alcoholic beverages / week or if a urine drug screen (Drug-Screen Multi 12-AE, Nal von Minden GmbH, Regensburg, DE) revealed drug abuse. All participants were shift workers, although specific shift schedules varied between individuals by occupation, such that emergency medical rescue workers and emergency doctors worked cycles of two 12-hour days followed by two 12-hour nights, terminating in four free days. Police officers worked four contiguous shifts with varying individual activity and bedrest times. Data on individual shifts were not collected or analyzed. Individuals received a monetary compensation for participating in the study. Participants additionally received a report on their sleep derived from their own sleep data derived from Fitbit Charge 2^{TM} and PSG. That report was explained to them by a study staff member.

Validated German translations of questionnaires administered at meetings at the start and upon completion of the one month of monitoring were used to assess lifestyle, psychological, and sleep variables, such as the following. The Pittsburgh Sleep Quality Index (PSQI) questionnaire measured subjective sleep quality over the past four weeks, with higher values indicating poorer sleep quality (range: 0-21). A cutoff score of $\geq$ 5 indicates sleep of poor quality (Buysse et al. 1989). Posttraumatic Stress Disorder (PTSD) Checklist for Diagnostic and Statistical Manual of Mental Disorders 5th Edition (PCL-5) questionnaire was used to assess subjective posttraumatic stress symptoms over the past month with respect to an experienced lifelong referent traumatic event of greatest adversity. Greater scores indicate greater posttraumatic stress. A cutoff score of 31-33 indicates probable PTSD diagnosis (Blevins et al. 2015). The Perceived Stress Scale 10 (PSS-10) measured subjective stress over the past month and scores range from 0-40, with higher scores indicating greater perceived stress; there is no cutoff score, but normative values are available by demographic population sampled (e.g., age, sex, race/ethnicity); mean ($\pm$ s.d) male and female scores are 12.1 $\pm$ 5.9 and 13.7 $\pm$ 6.6, respectively (Cohen and Williamson 1988). The Horne-Östberg Morningness-Eveningness Questionnaire – A Reduced Scale (rMEQ) assessed an individual's preferred rest-activity behavior or 'chronotype', with higher scores indicating increasing morning activity preference. Scores on the rMEQ range 4-25. Most (60%; scores: 12-17) individuals show neither an evening (20% of individuals; scores: 4-11) nor morning (20% of individuals; scores: 18-25) activity preference (Adan and Almirall 1991).

Polysomnographic recordings

A total of 62 individuals (43 emergency medical rescue workers; 16 police officers; 3 emergency doctors) of whom 56.45% were females completed two nights of ambulatory PSG recordings in their home. Their demographics are displayed in **Table 2.1**. The PSG recordings were always made of nocturnal sleep following a day work shift and consisted of an adaptation night (AN) and then a baseline night (BN) the following evening. Individuals were free to determine their bedtime and

duration of sleep episode. The AN served as a combined adaptation and screening night, whereas the BN provided the data analyzed in this report, with the exception of 8 individuals, whose data originate from the AN due to their data being of poor quality in the BN. Data from one individual were excluded from analyses due to the data being of poor quality on both nights. The total PSG sample consisted therefore of 61 individuals. On two nights, the Fitbit Charge ^{2TM} data sets for two individuals were not obtained, reducing the sample to 59 individuals who have both PSG and Fitbit Charge 2^{TM} data for comparison. Mean Fitbit and PSG derived sleep- and HR measures from these 59 individuals can be found in **Table 2.1**. All PSG data were acquired by dedicated ambulatory polygraphic amplifiers (SOMNOscreen^{TM} Plus, SOMNOmedics GmbH, Randersacker, DE). The overall PSG montage consisted of scalp electrode sites Fz, Cz, Pz, Oz, C3, C4, A1, A2 applied according to the EEG International 10-20 System (Jasper 1958) and electrooculogram (EOG), submental electromyogram (EMG) and ECG and grounding electrode according to American Academy of Sleep Medicine standards (AASM 2007). The Cz electrode served as the reference during recording, and the opposite mastoid was used for re-referenced display. The sampling rate of all sites was 256 Hz. For recording, high-pass (0.2 Hz) and low-pass filters (128.0 Hz) were used. Sleep stages were scored visually by an experienced individual (IC) in 20-s epochs according to AASM (2007) criteria. High-pass (0.3 Hz) and low-pass (35.0 Hz) filters in addition to a powerline filter were applied for visual sleep scoring.

The ECG trace in PSG recordings was examined visually one epoch at a time for all wake epochs before sleep onset and all epochs of sleep and wake after sleep onset. Artifacts and ectopic beats present in the ECG trace which had potential to interfere with the quantification of inter-beat intervals (IBI), defined as the time interval between the normal R peaks of the QRS complex, were manually marked and removed before data processing and analysis.

Table 2.1. Demographics, sleep, and heart rate variables

	Demographics Mean (SD)	Sleep and HR Mean (SD)	
		Polysomnography	Fitbit
Female [%]	56.5		
Police [%]	25.8		
Age	33.5 (8.1)		
BMI	33.5 (8.1)		
PSQI	5.8 (2.7)		
PCL-5	6.2 (7.9)		
PSS-10	12.2 (4.9)		
rMEQ	14.4 (3.5)		
$N1_{so}$ time of day [h]		23.4 (0.9)	23.4 (2.4)
TST [h]		8.0 (1.7)	7.8 (2.6)
REM_d [h]		1.7 (0.8)	1.7 (0.7)
$Light_d$ [h]		4.2 (1.1)	4.4 (1.3)
$Deep_d$ [h]		1.5 (0.6)	1.3 (0.5)
WASO [h]		0.4 (0.5)	1.0 (1.1)
REML [min]		76.3 (30.6)	103.9 (59.7)
REM in first cycle [%]		11.6 (8.1)	15.0 (8.7)
HR_{10} REM [bpm]		60.9 (9.1)	59.9 (8.2)
HR_{10} N1 [bpm]		61.8 (9.2)	59.2 (7.5)
HR_{10} N2 [bpm]		56.6 (7.7)	55.7 (7.0)
HR_{10} N3 [bpm]		58.8 (8.8)	57.2 (7.2)
$HRvar_{10}$ REM [bpm]		28.1 (90.8)	6.4 (16.1)
$HRvar_{10}$ N1 [bpm]		48.7 (110.1)	6.8 (16.7)
$HRvar_{10}$ N2 [bpm]		22.0 (76.7)	4.7 (24.3)
$HRvar_{10}$ N3 [bpm]		25.4 (111)	2.9 (12.9)

Demographics of the study sample (N= 59). Except for gender percentages the table provides the means and in brackets the standard deviations. Body mass index (BMI); Pittsburgh Sleep Quality Index (PSQI); Posttraumatic Stress Disorder (PTSD) Checklist for Diagnostic and Statistical Manual of Mental Disorders 5th Edition (PCL-5) The Perceived Stress Scale 10 (PSS-10) ; The Horne-Östberg Morningness-Eveningness Questionnaire – A Reduced Scale (rMEQ); beats per minute (BPM); Rapid eye movement (REM) sleep; non-rapid eye movement sleep stages 1 (N1), 2 (N2) and 3 (N3); total sleep time (TST); wake after sleep onset (WASO); REM latency (REML); 10%-trimmed heart rate average (HR_{10}); 10%-trimmed heart rate variability ($HRvar_{10}$); Sleep onset with N1 criteria ($N1_{so}$); REM sleep duration (REM_d); light sleep or N1 + N2 duration respectively ($Light_d$) and deep sleep or N3 duration respectively ($Deep_d$).

Fitbit Charge 2™ recordings

The Fitbit Charge 2™ was continuously worn by all participants during the PSG recorded nights. The device records wrist activity by means of accelerometry and pulse via photoplethysmography (PPG). It produces two types of sleep data depending on whether certain criteria are fulfilled during data

collection. These criteria are sufficient battery charge, a sleep episode > 3 hours in duration, and sufficient skin contact to the PPG sensor. If these criteria are not fulfilled, then "classic" sleep data are generated, comprising "asleep", "awake" and "restless" variables at a 1-min data granularity. If criteria are fulfilled, then "stages" data are produced, comprising "wake", "light", "REM" and "deep" sleep at a 30-s data granularity. If "stages" data are obtained for a given sleep episode, then users receive two data sets, i.e., (1) sleep data, which is composed of stages and (2) wake data, which is composed exclusively of wake episodes < 30 s. Both data sets are present in a single .json file for a given date of data collection. There are also wake episodes contained within the sleep data set, however. The variable WASO was created in the present report by merging these two data sets contained within "stages" data type output. The Fitbit sleep staging algorithm occasionally scores the first stage after S_{on} and the last stage before S_{off} as "wake." This runs counter to an intuitive definition of S_{on} and S_{off} as the first occurrence of sleep and last occurrence of sleep, respectively. We manually omitted such bordering wake episodes and adjusted the S_{on} and S_{off} values accordingly. A sleep sensitivity setting is needed to be set for Fitbit's sleep recordings, with options "sensitive" and "normal". When set to 'normal', only major body movements, such as rolling over, will register as wake, whereas when set to 'sensitive' more subtle movements will additionally be registered as wake. We set the setting to "sensitive" throughout data collection.

Statistical Analyses

All analyses and data-processing steps were carried out in the programming language *R* (version 4.0.0) (R Core Team 2020). Fitbit intraday HR measures were used. For the ECG R-peak detection, the Pan-Tompkins algorithm (1985) was used as implemented in the *rsleep* package (version 1.0.3). The algorithm was not able to distinguish sharp T waves from R peaks on various occasions, however. Thus, a modification to the algorithm had to be made. The signal can sometimes be inverted in the sign, and for this reason we changed the signal to have positive R-peaks (which was revealed by the mean of the detected peak values by the Pan Tompkins algorithm). Sometimes the peak can be slightly misaligned with the actual R peak maximum. Therefore, after running the Pan-Tompkins algorithm, the detected peak was aligned with the actual maximum ± 200 ms around the detected peak. Furthermore, in cases where two peaks were observed within less than 360 ms, we checked if the subsequent peak was a mistakenly detected T-wave or an actual R-peak. We did this by visually examining a small window of ± 28 ms around the detected and maximally aligned peak and took smaller second derivatives, which indicated slower changes in the tangents of the ECG signal, as an indication of a T-wave as compared to faster tangent changes from R peaks. The 60%-quantile of the absolute value of the second derivative ($QAVSD_{60}$) was then compared to a cut-off point specific to an individual participant derived by the density function of the $QAVSD_{60}$ values from all the detected

peaks of the individual. The cut-off point was defined as the first local minimum of the density within the hard limits 35/256 $\mu V/s^2$ and 120/256 $\mu V/s^2$. If no local minimum was present, the value 35/256 $\mu V/s^2$ was used instead. The density of $QAVSD_{60}$ revealed a multimodal distribution of nearly no overlap between T-wave characteristic $QAVSD_{60}$ values compared to ones originating from R-peaks. Erroneously detected T-waves were omitted, thereby rescuing these affected segments of ECG data sets for subsequent analyses. This small T-wave check and alignment of the peak to the local maximum improved algorithm performance significantly on visual inspection. From PSG IBIs a transformation into beats per minute was made with 60 s divided by the IBI duration in seconds. The internal clock times of the Fitbit app and the PSG system were misaligned. Hence, we estimated a time-shift for each individual to assure a correct time alignment. For this, a linear interpolation was used to estimate values between two datapoints in either the PSG beat-per-beat data or the lower resolution Fitbit data. We resampled both the Fitbit and PSG interpolated time series of a given night at 0.2-s intervals. The cross-correlation Function was used to extract the lag with maximal correlation between the time series.

Bland-Altman plots were made with the *blandr* package (version 0.5.1) for all the sleep variables, t-tests and LoA defined as $b \pm 1.96 \cdot SD$, where b denotes the bias and SD the standard deviation of the bias. A variable is termed as "unbiased" if the bias b is not significantly different from 0 from the according t-test. The differences in the Bland-Altman analyses were set to denote PSG *minus* Fitbit. Thus, a positive difference corresponds to an underestimation of Fitbit compared to PSG and a negative difference corresponds to an overestimation. Concerning the repeated measurements of 10%-trimmed HR average (HR_{10}) and 10%-trimmed HR variance ($HRvar_{10}$) as measured in 1-min intervals, a linear mixed effects regression (LMER) with the *nlme* package (version 3.1-147) was estimated. The dependent variable was set to be the PSG-Fitbit values and just a single intercept without a slope was taken for the independent variable. As for the random effect, a random intercept per subject was included. Due to having consecutive 1-min HR_{10} and $HRvar_{10}$ measurements with potential time correlations, an autocorrelation structure of order one was added. The t-tests and LoAs were estimated from the mixed model.

EBE analyses were performed through the statistical measures: sensitivity = TP/P, specificity = TN/N, accuracy = $(TP + TN)/(P + N)$, Matthews correlation coefficient (MCC) = $(TP * TN - FP * FN)/\sqrt{(TP + FP) * (TP + FN) * (TN + FP) * (TN + FN)}$, positive predictive value (PPV) = $TP/(TP + FP)$ and negative predictive value (NPV) = $TN/(TN + FN)$, where TP denotes true positives (number of Fitbit epochs that share a given PSG stage), TN = true negatives (the number of Fitbit epochs that are not in a given stage and where the according PSG epoch is also not labelled as that stage), FP = false positives (number of Fitbit epochs that do not share a given PSG stage), and FN = false negatives (number of Fitbit epochs that do detect a given stage while PSG did

not detect it). Sensitivity measures the proportion of epochs of a given PSG derived sleep state that was correctly identified by Fitbit (e.g., for REM sleep it is the percentage of Fitbit "REM" sleep stages among all PSG REM sleep stages). Specificity, on the other hand, describes the percentage that Fitbit correctly identifies the non-occurrence of a given sleep state. Accuracy is a combined measure of the true discoveries and true negatives of Fitbit divided by all positives and negatives in the PSG sample. MCC is considered a more informative measure than accuracy as it takes all TP, TN, P and FN into account. It can be interpreted like a correlation coefficient, i.e., the more positive, the better Fitbit predicts the PSG epochs, such that 0 would be random guessing, and negative values indicate disagreement. PPV, often called the precision, describes the proportion of Fitbit correctly identifying a given stage amongst the number of times Fitbit assigned that stage, and respectively NPV describes the equivalent for correctly identifying an epoch not to be a given stage. In our sample, the epoch length is defined as 20 s, but Fitbit's algorithm has an epoch length of 30 s. Thus, a direct EBE analysis was not possible. Therefore, we looked at all PSG derived epochs and compared them to the dominating Fitbit stage (>50%) in the same interval. In cases where one PSG epoch contained two different Fitbit stages of equal length, we chose the first stage.

Results

Time alignment

Accurate temporal synchronization between the PSG system and the wearable Fitbit device often poses a methodological challenge in validation studies. This was also the case here. When scrutinizing our data, we noticed that the time discrepancies between the PSG system and the Fitbit application's clocks increased as the study went on. In other words, the later the participant entered the study, the higher the time difference between PSG and Fitbit recordings was. This relationship can be seen in **Figure 2.1** as a linear association between the individual participant identifier number and the estimated time-shift between the two measurement instruments. To align the time series, we computed the cross-correlation function for each participant and corrected the time shift by the emergent maximum. Our time alignment efforts produced good correspondence in our data between the two instruments, as evident in the simultaneous occurrences of HR bursts in the two time series (**Figure 2.2**). Nevertheless, the variability and the amplitude of the Fitbit curve was reduced compared to PSG because only between 4 and 12 measurements per minute were made available by Fitbit. The analysis of the entire Fitbit sample revealed that an average of 7.38 HR counts per minute was available (**Figure 2.3**). By contrast, PSG HR data were sampled with a frequency of 1/256 Hz.

Figure 2.1 PSG-Fitbit time shift

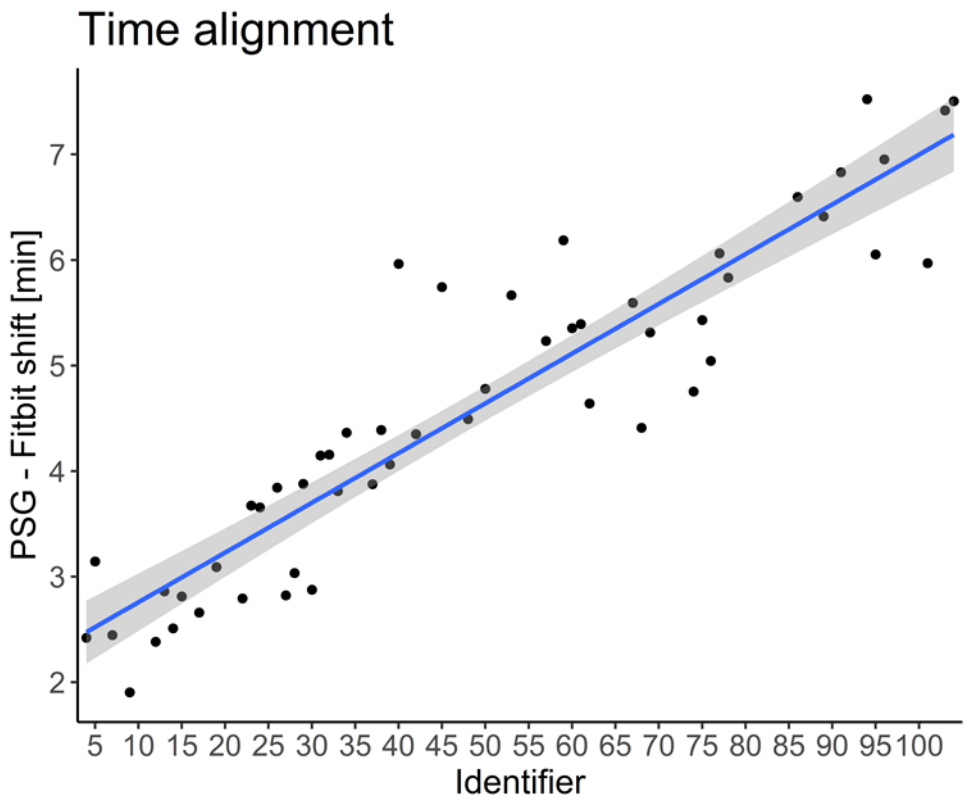

Figure 2.1: The participant identifying number, where higher numbers indicate chronologically later entry into the study from the entire study sample, is shown on the x-axis and on the y-axis the data-driven timeshift between PSG and Fitbit is displayed. There is a significant linear relationship between the identifier and the shift ($p < 0.001$, adjusted $R^2 = 0.85$). Thus, the times drifted apart as the study went on, with a minimum time misalignment of 1.9 min and a maximum of 7.5 min.

Figure 2.2 PSG-Fitbit data time shift

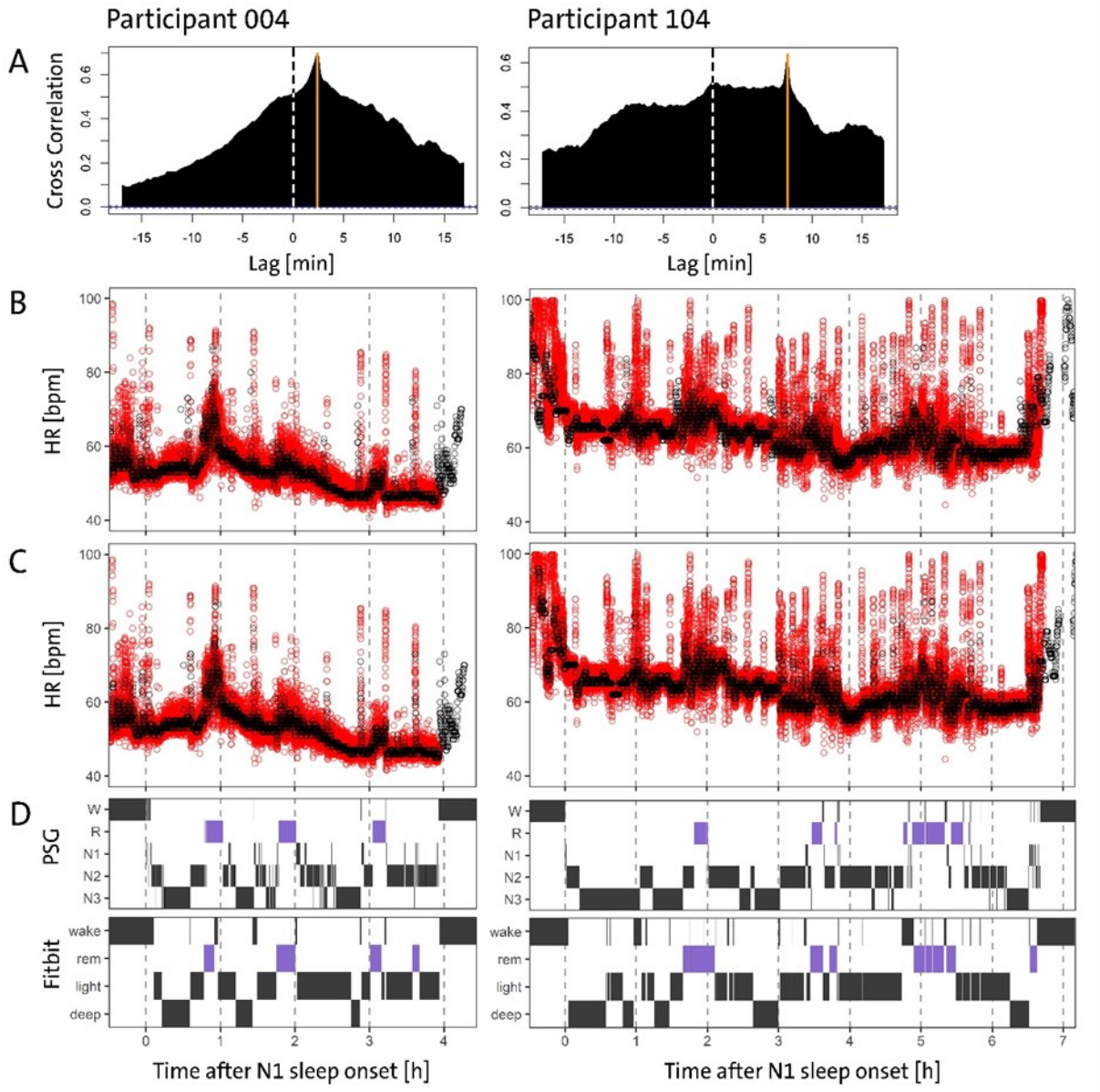

Figure 2.2: The validation night of the first participant in the study with identifying number 004 (left column) and the last participant in the study with number 104 (right column) are shown. Row A displays the cross-correlation function, displaying a large visible maximum at the orange vertical line representing the best alignment between the two devices (PSG and Fitbit). The dashed vertical reference line shows a lag of 0 min. Rows B-D share the same x-axis denoted as hours after PSG derived sleep onset with N1 criteria. For each hour in the recording a vertical dashed grey line was added. In row B the HR in bpm derived from PSG (red) and Fitbit (black) are shown as seen before any time alignment was applied, whereas row C presents the HR data after the data-driven shift from panel A was applied. The time aligned time series visually show good agreement after correcting for the time difference. Fitbit shows reduced variability in the signal, but with fairly good average correspondence. In panel D, the top row shows PSG derived hypnograms for both participants, whereas in the bottom row the Fitbit derived hypnograms are displayed. All hypnograms have been time-corrected according to panel A. The overall sleep structure is captured reasonably well by Fitbit, but Fitbit detects more "wake" and "rem" episodes compared to PSG and the distinction of "light" (N1+N2) and "deep" (N3) sleep often seems to be particularly challenging for Fitbit.

Distribution of sleep stage durations

Next, we compared the distribution of sleep stage durations between Fitbit and PSG data (**Figure 2.4)**. A duration was defined as the duration of consecutive epochs with the same sleep stage until interrupted by any other stage independent of its duration. We observed that Fitbit uses 30 second intervals to classify the "stages" data, whereas the "classic" data are presented with less time-resolved, 1-min resolution. With respect to wake episodes, the Fitbit data resemble the PSG distribution, with mostly short uninterrupted wake episodes and much rarer longer episodes. The "awake" category in the "classic" datatype has higher tails, possibly due to having a resolution of 1 minute instead of 30 s, thus potentially missing certain stage changes that occur faster. Fitbit's "light" sleep stage in the "stages" datatype probably refers to N1 and N2 PSG stages, whereas "deep" sleep may refer to the N3 PSG sleep stage. Any definition, however, cannot be known without doubt because this information is not provided by Fitbit. In any case, "light" and "deep" sleep show longer tails compared to all non-rapid eye movement (NREM) PSG sleep episodes possibly due to different temporal resolutions or slower changes in HR and HRV compared to the more sudden changes in brain states. Furthermore, the "deep" sleep distribution shows a pronounced discontinuity at around 4 min and 30 s which can also be observed in the Fitbit "REM" sleep stage duration. The distributions of "light," "deep" and "REM" sleep show discrepancies to the PSG derived durations indicating that the algorithm does not fully reflect PSG derived data and might miss brief stage changes and stage interruptions. Furthermore, it is unknown what the "restless" stage in the "classic" datatype refers to. This stage displays a peak at around 11 min, with unknown origin.

Figure 2.3 Fitbit HR measurements

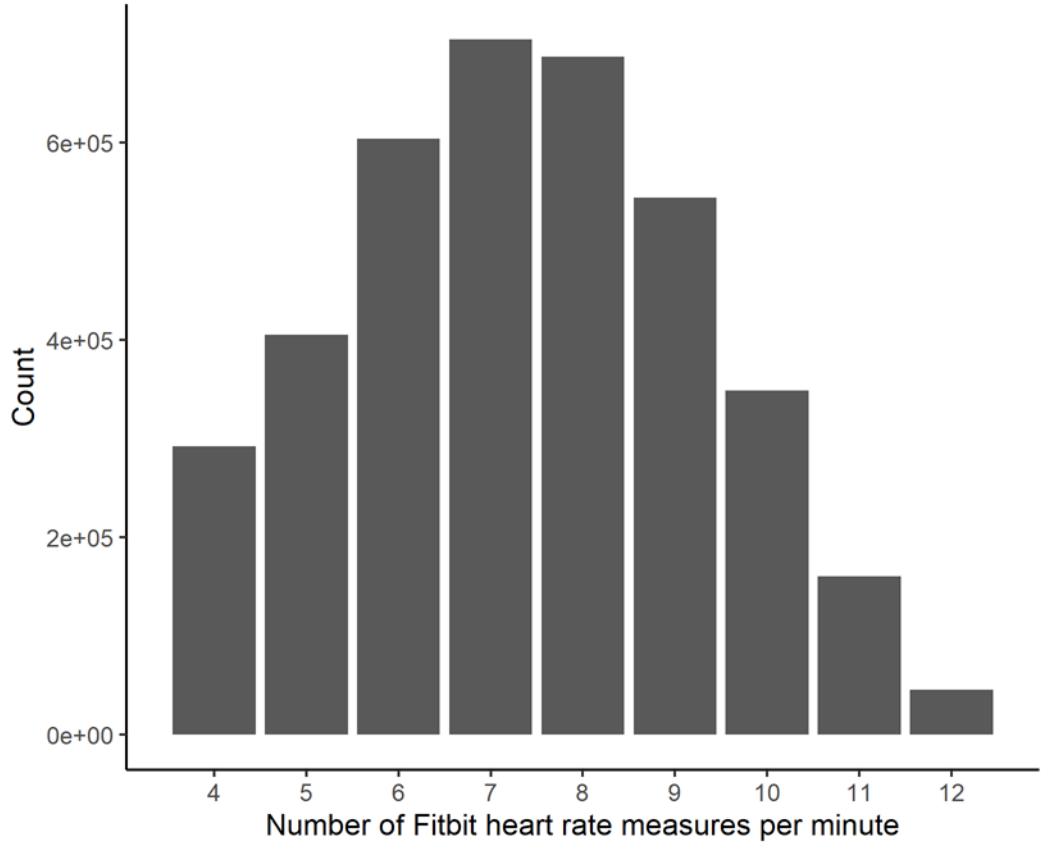

Figure 2.3: From the larger study (n = 89), with duration of one month of continuous Fitbit HR data, all single minutes of available data were extracted and counted for number of HR measures contained. This bar plot thus consists of 3'797'608 individual minutes of data. This roughly amounts to the expected total minutes of 3'844'800 = 89 subjects * 30 days * 24 hours per day * 60 minutes per hour, especially after considering the missing time periods, for example when taking off the device to take a shower, synchronize with the Fitbit app or recharge or for individuals who elected simply not to wear the device for undisclosed reasons. We see that Fitbit provides on average 7.37 measures per minute. There was some number of measurements per minute above 12 and below 4, but they were so small that the bar plot displayed no visible height and are for the sake of clarity not displayed.

Figure 2.4 Distribution of sleep stage durations for Fitbit and PSG

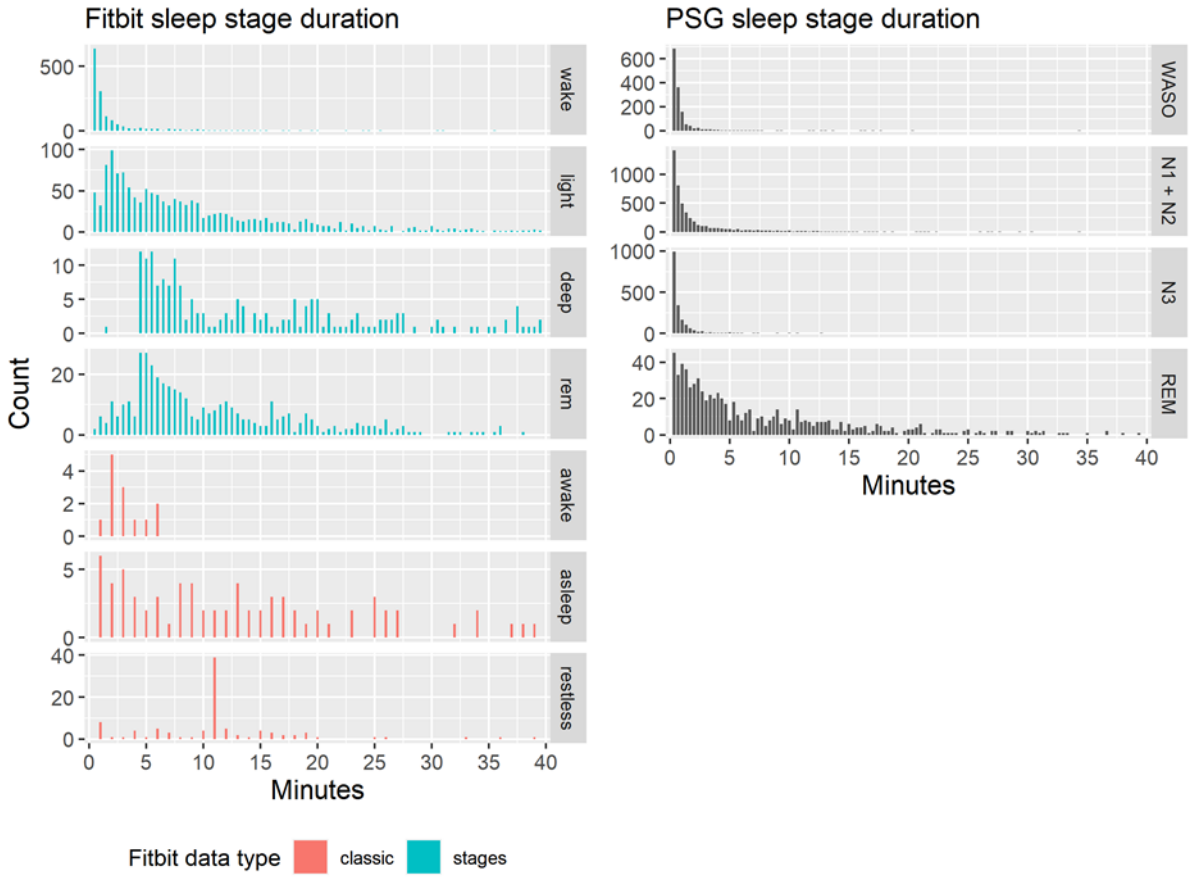

Figure 2.4: The distribution of sleep stage durations for Fitbit (left panel) and PSG (right panel) both computed on the sample of the nights used for validation. Here the plot has been cut off at 40 min for visual purposes, the tails continue to decrease as one would expect. Fitbit sleep staging data types "classic" (red) and "stages" (blue) show large deviations compared to PSG sleep stages (black). Especially "deep" and "rem" sleep show non-biological discontinuity around 4:30 min, and all Fitbit stages have larger tails. The stage "restless" has a peak at 11 min with unknown meaning.

Bland-Altman analyses of sleep variables

We split our validation into two analyses, one with the PSG-determined first occurrence of N1 sleep as criterion for sleep onset ($N1_{on}$) and the other with the first occurrence of N2 sleep as criterion for sleep onset ($N2_{on}$). This was done because it is unknown how Fitbit estimates sleep onset. In **Figure 2.5** we plotted the variables computed with $N1_{on}$ and **Table 2,2** provides the associated statistics. Sleep onset defined as $N1_{on}$ is unbiased (-1.6 min, $p = 0.731$) whereas $N2_{on}$ displays a higher bias of 6 min ($p = 0.209$). S_{off}, TST, REM_d, the duration of Fitbit's "light" sleep in minutes ($light_d$) interpreted as N1 + N2, and the duration of Fitbit's "deep" stages in min ($deep_d$) did not display significant bias for both sleep onset criteria. Nevertheless, $deep_d$ shows a trend towards a bias of 11.2 min with $N1_{on}$ ($p = 0.078$) likely pointing to a slight underestimation with Fitbit of N3 sleep. REM sleep latency (REML) and WASO both exhibit a significant overestimation with Fitbit when relying on $N1_{on}$: REML was overestimated by 29.4 min and WASO by 37.1 min ($p_{all} < 0.001$). When relying on $N2_{on}$,

the biases in absolute terms are generally larger. Even though the marginal densities of the differences for S_{on}, S_{off}, and TST are quite narrow, being indicative of a good estimator in general, some occasional sleep episodes can disagree strongly between the Fitbit and PSG instruments as reflected in the large LoA (**Table 2.2**). The marginal distributions of REM_d, $light_d$, and $deep_d$ show higher variance even if outliers are neglected. This observation may indicate that the estimation of stages of sleep is challenging for Fitbit's algorithm and a source of variability, even while being unbiased.

Table 2.2. Bland-Altman Statistics

	$N1_{on}$				$N2_{o}$	
Variable	PSG-Fit	lower LoA	upper LoA	p-value	PSG-Fit	lower LoA
S_{on} [min]	-1.6	-68.8	65.6	0.731	6	-62.9
S_{off} [min]	-5.6	-189.3	178.2	0.659	-5.6	-189.3
TST [min]	-4.0	-204.3	196.3	0.772	-11.5	-212.1
REM_d [min]	-2.7	-87.8	82.4	0.673	-2.9	-88.6
$Light_d$ [min]	-10.4	-136.8	116.0	0.270	-14.7	-142.6
$Deep_d$ [min]	11.2	-72.9	95.2	0.078	10.5	-74.8
WASO [min]	-37.1	-188.1	113.8	0.001	-39.7	-188.8
REML [min]	-29.4	-145.4	86.6	0.001	-36.8	-162.9
	HR_{10} [bpm]				$HRvar_{10}$	
Overall	0.9	-6.9	8.6	0.000	20.3	-82.1
WASO	1.9	-5.4	9.2	0.028	60.2	-81.0
N1	1.2	-8.9	11.3	0.137	51.1	-180.4
N2	0.6	-4.7	6.0	0.001	17.6	-53.3
N3	0.6	-6.4	7.6	0.008	16.3	-85.0
REM	0.7	-4.7	6.0	0.000	18.5	-63.5

Statistics accompanying Bland-Altman plots (**Figure 2.5**). For sleep onset (S_{on}), sleep offset (S_{off}), total sleep time (TST), REM sleep duration (REM_d), Fitbit light sleep or PSG N1+N2 sleep duration respectively ($light_d$), Fitbit deep sleep or PSG N3 sleep duration respectively ($deep_d$), wake after sleep onset (WASO) and REM sleep latency (REML), two column-blocks are shown with S_{on} and REML calculated with N1 or N2 sleep onset criteria ($N1_{on}$ respectively $N2_{on}$). Average 10%-timmed heart rate (HR_{10}) and 10%-trimmed heart rate variance ($HRvar_{10}$) values in various sleep states are presented in the columns below the sleep variables. The average difference between PSG and Fitbit measures the bias and can be found in the first column. The lower and upper LoA describe 1.96 times the standard deviation around the bias and can be found in the subsequent columns. In the last column of each $N1_{on}$ or $N2_{on}$ block, the p-value for the paired t-test is reported, testing whether the bias is significantly different from 0. The various shades of green (darker colors corresponding to smaller *p*-values) highlight significant ($p < 0.05$) biases.

Bland-Altman analyses of HR variables

The Bland-Altman plots for the HR variables are shown in **Figure 2.6**. When computing the interval between 30 min before $N1_{on}$ until S_{off} without taking into account the different wakefulness and sleep states, HR_{10} and $HRvar_{10}$ measures both appear biased. More specifically, Fitbit underestimated HR_{10} overall by 0.9 bpm and displayed LoA of -6.9 and 8.6 bpm (**Table 2.2**). This is a rather small

underestimation, with a relatively narrow marginal distribution of the differences. When focusing on 1-min HR_{10} values restricted to the time interval between S_{on} and S_{off} and dividing among the PSG derived states N1, N2, N3, REM sleep, and wake, HR_{10} displayed a higher bias in wake (1.9 bpm, p = 0.028) and N1 (1.2 bpm, p = 0.137) when compared to the sleep stages N2 (0.6 bpm, p = 0.001), N3 (0.6 bpm, p = 0.008), and REM sleep (0.7 bpm, $p < 0.001$).

When analyzing overall HR variance, Fitbit strongly underestimated $HRvar_{10}$ with a bias of 20.3 bpm ($p < 0.001$), which is associated with higher LoA -82.1 and 122.7. When $HRvar_{10}$ was divided among the different sleep stages, we observed behavior similar to HR_{10}, such that $HRvar_{10}$ wake and N1 had a higher bias (60.2 and 51.1 bpm) than N2, N3, and REM sleep (17.6, 16.3 and 18.5 bpm) all with low p-values and considerably large LoA.

Figure 2.5 Bland-Altman plots for sleep variables

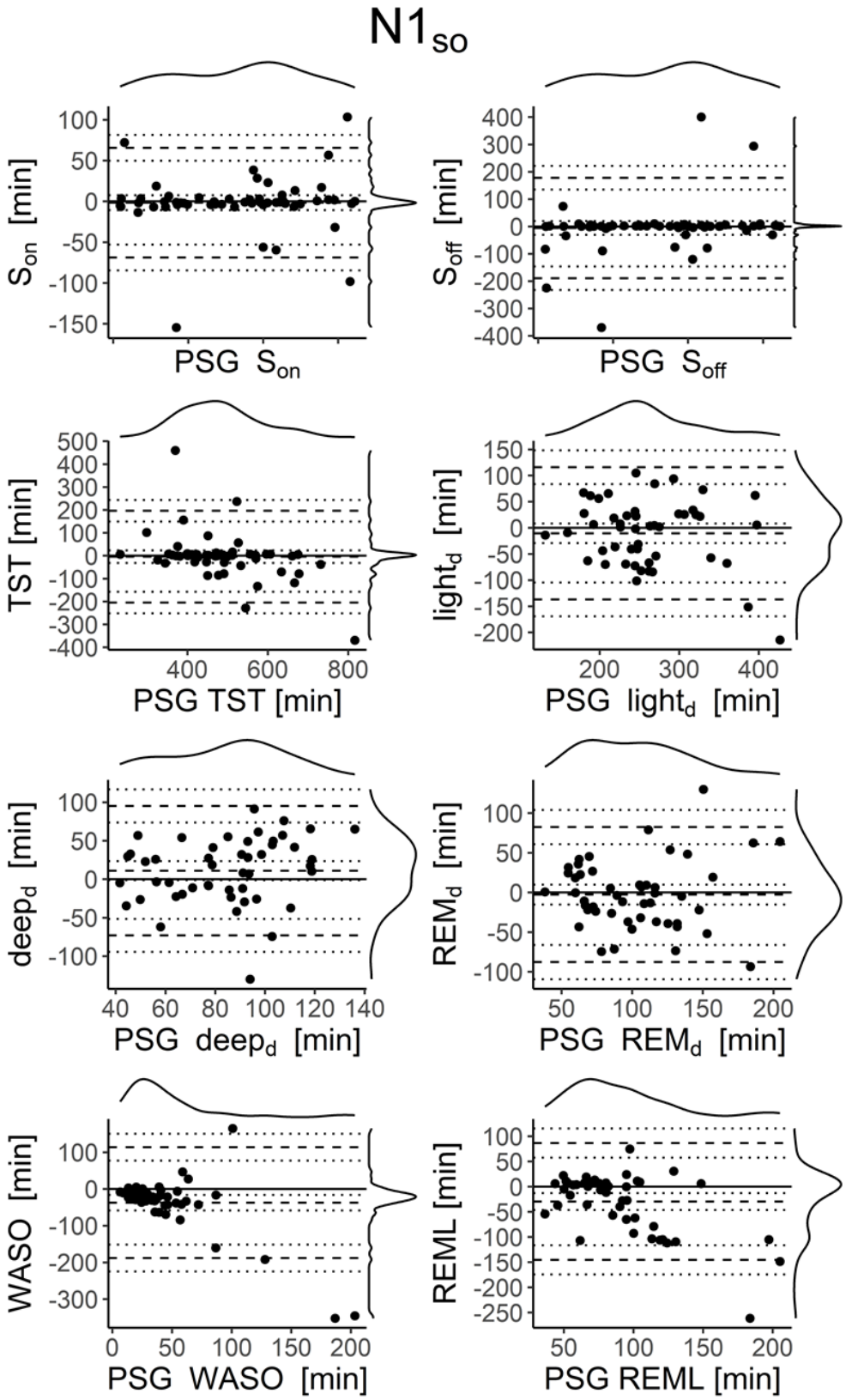

Figure 2.5: Bland-Altman plots for various sleep variables are shown with sleep onset defined as the first occurrence of N1. The dashed lines denote lower Limits of Agreement (LoA), bias and upper LoA. The dotted lines are the respective 95% confidence intervals of LoA. On the top and right of each panel the marginal densities are plotted. The x-axis displays the PSG variables, and the y-axis denotes the differences of the two devices (PSG - Fitbit). N1 derived sleep onset is unbiased. Sleep offset (S_{off}), total sleep time (TST), light sleep or N1 + N2 sleep duration respectively ($light_d$), deep sleep or N3 sleep duration ($deep_d$), and REM sleep duration (REM_d) do not have significant bias. Wake after sleep onset (WASO) and REM sleep latency (REML) display a significant deviation of the difference between the devices from 0.

Figure 2.6 Bland-Altman plots for heart rate variables

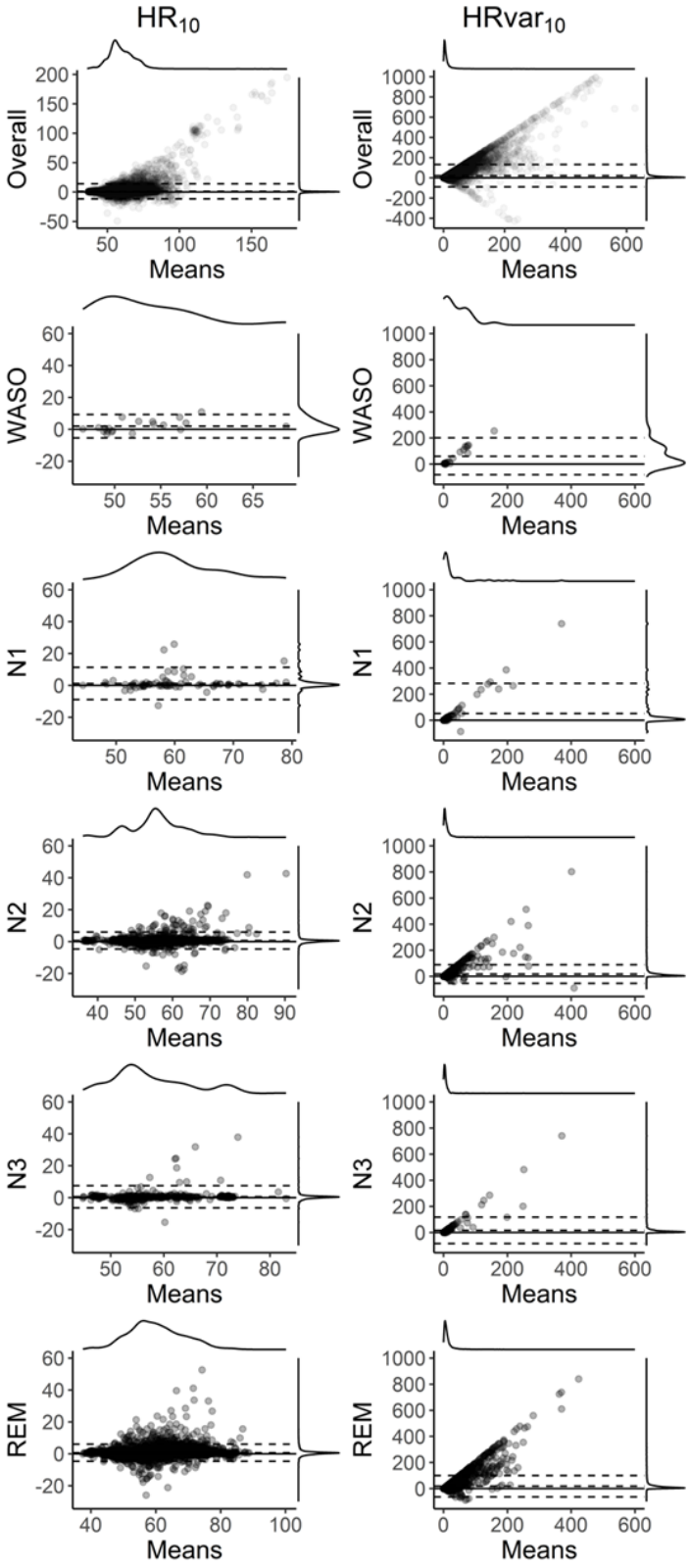

Figure 2.6: Bland-Altman plots for HR derived variables. The dashed lines denote lower LoA, bias and upper LoA for a mixed model dealing with the repeated measures. On the top and right of each panel are the marginal densities. The x-axis displays the means of both devices, meaning (PSG + Fitbit)/2, and the y-axis denotes the differences of the two devices (PSG - Fitbit). Overall average 10%-trimmed HR (HR_{10}) and 10%-trimmed HR variance ($HRvar_{10}$) values are calculated for one-minute intervals between 30 min before sleep onset (S_{on}) with N1 critera and 30 min after sleep offset (S_{off}), all other variables are calculated between S_{on} and S_{off} only extracting the designated variable, again calculated in one-minute intervals.

Epoch by epoch (EBE) Analysis

The EBE comparison between Fitbit and PSG revealed that Fitbit displays better specificity (WASO 0.898, light sleep as N1+N2 0.574, deep sleep as N3 0.92, REM sleep 0.889) than sensitivity (WASO 0.428, light sleep as N1+N2 0.534, deep sleep as N3 0.279, REM sleep 0.548). Sensitivity for REM sleep was worse during the initial 120 min of sleep (0.432) when compared to REM episodes beginning 120 min or more after sleep onset (0.57). By contrast, for specificity, this relationship was reversed (REM < 120 min 0.963, REM > 120 min 0.864). Accuracy was best for WASO (0.898) and REM sleep (0.880) and worse for deep sleep as N3 (0.776) and light sleep (N1 + N2) (0.553). A similar relationship was reflected in the MCC, ranging from weak to moderate correlation (REM sleep 0.339, WASO 0.329, deep sleep as N3 0.25, light sleep as N1+N2 0.108). The MCC measure is preferrable over accuracy, as it only leads to higher scores if the prediction is simultaneously accurate in all confusion matrix categories (TP, FP, TN, FN) (Chicco and Jurman 2020). The PPV, the probability that an episode with a given Fitbit stage will also have the same PSG stage, was generally lower (WASO 0.438, light sleep as N1+N2 0.592, deep sleep as N3 0.501, REM sleep 0.306) compared to the NPV, the probability than an episode that does not have a certain Fitbit stage will also not have that PSG stage (WASO 0.894, light sleep as N1+N2 0.516, deep sleep as N3 0.815, REM sleep 0.956).

Table 2.3.

State	Sensitivity	Specificity	Accuracy	MCC	PPV	NPV
WASO	0.428	0.898	0.824	0.329	0.438	0.894
Light sleep	0.534	0.574	0.553	0.108	0.592	0.516
Deep sleep	0.279	0.920	0.776	0.250	0.501	0.815
REM sleep	0.548	0.889	0.861	0.339	0.306	0.956
REM sleep < 120 min	0.432	0.963	0.934	0.383	0.403	0.967
REM sleep > 120 min	0.570	0.864	0.837	0.329	0.296	0.953

Epoch-by-Epoch (EBE) comparison of Fitbit and PSG stages. For each stage, wake after sleep onset (WASO), light (N1+N2), deep (N3), REM, where REM sleep was divided into analyses with REM sleep episodes occurring during the first 120 min after sleep onset with N1 criteria ($N1_{on}$) and REM sleep episodes that occur later than 120 min after $N1_{on}$ Various performance measures were used, including sensitivity, specificity, accuracy, Matthews Correlation Coefficient (MCC), Positive Predictive Value (PPV) and Negative Predictive Value (NPV). More information on these measures can be found in the methods section. Fitbit shows mostly good specificity but bad sensitivity. The accuracy is relatively high, except for light sleep. The MCC displays a moderately positive relationship, with light and deep sleep being considerably less good. NPV is usually higher than PPV.

Discussion

We evaluated the performance of the multi-sensor wearable Fitbit Charge 2™ against PSG of the sleep macrostructure and HR in a sample of first responder shift workers under naturalistic conditions. We observed that S_{on}, S_{off}, TST, REM_d, N1 + N2 sleep duration, and N3 sleep duration revealed unbiased estimates but with non-negligible LoA. Fitbit overestimated REML by -29.4 min, possibly because the proprietary algorithm failed to detect very short first REM sleep episodes. This hypothesis is supported by the right shift of the maximum in duration of stages and larger tails (**Figure 2.4**) and a cluster of REML data points occurring at approximately -100 min (**Figure 2.5)**, indicating that Fitbit cannot capture short lasting stage durations well. Not only REML but also the other sleep variables often exhibited wide LoA. In addition, despite performing a careful, data-driven time-alignment between the Fitbit and PSG time series which differed from 1.9 min to 7.5 min depending on the participants' entrance into the study, Fitbit overestimated WASO by as much as 37.1 min. We concluded that the unbiased sleep variables permit average estimations of important sleep quality characteristics in ecological conditions, yet the wide LoA in most variables and the large biases in REML and WASO limit the meaningfulness to quantify individual sleep episodes. These findings highlight the considerable challenges that are still present when relying on consumer grade technology to address clinical and research questions.

One of our most striking and novel findings is that the distribution of all sleep episode durations differs between the Fitbit Charge 2™ and polysomnography. Fitbit's sleep staging algorithm probably treats "REM" and "deep" sleep states of less than 4.5 min differently than sleep stages exceeding this duration. This introduces a non-biological discontinuity, indicating potential limitations of the tracker's staging algorithm. Furthermore, it is not clear what PSG measurement corresponds to the Fitbit stage "restless", which renders meaningful comparisons impossible.
The S_{on} measures from Fitbit are unbiased with respect to $N1_{on}$ criteria, whereas there is a higher but non-significant underestimation for $N2_{on}$. Thus, it is likely that Fitbit's definition of S_{on} time roughly corresponds to PSG derived $N1_{on}$. Sleep onset criteria should be reported in future validation studies because whatever criterion one selects (e.g., $N1_{on}$, $N2_{on,}$ or alternatively any stage of sleep) will impact many sleep variables, such as TST, REML and WASO, whose operational definition and calculation depend upon the criterion of sleep onset. This may be one of the reasons for discrepancies reported in the validation literature. One peculiarity of the staging information provided by Fitbit is that the first stage after the S_{on} time and the last stage before S_{off} time is sometimes staged as "awake" or "wake". We manually adjusted the S_{on} and S_{off} times, to be delineated by the first and last occurring stages of sleep rather than including stages of wake at the boarder of sleep. In a large Fitbit data set collected in 89 individuals over 1 month capturing roughly 3000 sleep episodes (Clark et al., in prep.), in 69.8% of all sleep episodes the first stage after S_{on} and in in 50% of all cases the last stage before

S_{off} was not coded as a sleep stage. In other words, an appreciable proportion of Fitbit sleep episodes are 'bookended' by a stage of wake. This is an inconspicuous but nevertheless important caveat. Our adjustment of these data could be one reason why we find $N1_{on}$, S_{off}, and TST to be unbiased when comparing Fitbit data to PSG data, whereas Liang et al. (Liang and Alberto Chapa Martell 2018), De Zambotti et al. (2018) and Morena-Pino et al. (2019) found TST biases in differing directions. Our correction also affects the WASO and REML measures and may contribute to an inconsistency of WASO when comparing our findings to others in the literature. More specifically, one previous study found unbiasedness (de Zambotti et al. 2018), another reported an overestimation of WASO (Liang and Alberto Chapa Martell 2018), while (Moreno-Pino et al. 2019) found an underestimation of WASO when validating Fitbit Charge 2™ against PSG. The study by (Liang and Alberto Chapa Martell 2018) with a WASO bias of 24.5 min is closest to our results of 37.1 min.

The information Fitbit provides on the sleep sensitivity setting, with options "sensitive" and "normal", may have an influence on the amount of stages that are scored as wake (Fitbit Inc. 2020a). We set the setting to "sensitive" when data were collected, which might have led to an overestimation of WASO as seen in Figure 2 panel D. However, Fitbit states that this setting has no impact in devices utilizing HR to track sleep (AndreaFitbit 2019). Consistent with our results, REM_d was also found to be unbiased by (de Zambotti et al. 2017). We additionally found $light_d$ and $deep_d$ to be unbiased. Since the algorithm is not open source, we do not know with certainty whether our study was running on an updated version of the algorithm compared to other validation studies. This limitation makes it difficult to compare validation study outcomes of consumer fitness trackers in general (de Zambotti et al. 2019) and could contribute to the discrepancies with the previous literature. Another reason might stem from the different population sampled or recording conditions. For example, the algorithm might be better suited to assess sleep in healthy individuals than in patients or in shift workers or may perform better in a sleep laboratory than in a naturalistic environment. The discrepancies underscore the need for standardized testing of consumer sleep technology to benefit from the powerful opportunities for large scale sleep data collection in ecological conditions (Karlen and Floreano 2011; Karlen et al. 2008; Menghini et al. 2020).

With respect to the HR data, Fitbit slightly underestimated overall HR_{10} by 0.9 bpm with a limited capability to capture sudden HR changes. This underestimation was smaller in N2, N3, and REM sleep stages (0.6, 0.6 and 0.7 bpm, respectively) compared to N1 sleep and wake (1.2 and 1.9 bpm), thus indicating a sleep stage-specific bias. The bias is low and probably not of biological relevance. The low *p*-values of biases in differences in the HR measures between the devices arise from the repeated measure design, since a vast number of 1-min values over the whole night for each subject was calculated, thereby increasing the statistical power to detect small biases as significant. The evident HR bias of 0.9 bpm is strikingly similar to the HR bias of 0.88 bpm found in (de

Zambotti et al. 2016) in the related Fitbit Charge HR™ device. As mentioned in the report by Haghayegh et al. (2019a), Fitbit Charge HR™ and Fitbit Charge 2™ share the same hardware and software, thus making a comparison feasible, software updates notwithstanding. We found a stage-dependent bias with lower underestimation in deeper sleep stages sharing lower HR on average and a larger underestimation in wake and the more transitory sleep stage N1, which share higher HR values on average, a finding compatible with the HR-dependent bias reported by Haghayegh et al. (2019a). For a HR during sleep of less than 50 bpm, these authors found an overestimation of 0.51 bpm and for a HR during sleep of greater than 80 bpm, an underestimation of 0.63 bpm. These values are comparable to our findings. On the other hand, Benedetto et al. (2018) found an HR underestimation of 5.9 bpm during wake. We also found a larger underestimation during wake episodes of 1.2 bpm, but not as high as 5.9 bpm. In the study by Benedetto et al. (2018), no time-alignment between the two instruments was reported. The method of capturing HR via video recording of live values displayed on the Fitbit app was innovative but could be a source of error. Hence, the results could potentially be influenced by a time misalignment between instruments and data collection methods. Fitbit HR variance was reduced due to inaccessibility of raw data and showed higher LoA than the LoA for HR. The differences between the assessments are not surprising, given that Fitbit only provided 7.4 measurements per minute on average (**Figure 2.3**). This is probably due to their algorithm providing some averaged values in preferably 5s, 10s, 15s measurement intervals (but other interval lengths, e.g., 2s or 7s intervals, can also be found in the data). For comparison, a PSG derived HR value can be computed for each inter beat interval. Thus receiving already pre-processed data from Fitbit instead of raw data naturally leads to a considerably higher variance in PSG recordings. Moreover, all HR values from Fitbit are integers, whereas the values from PSG are real values. This difference in the nature of the values (rounding to integers) additionally leads to slightly different behavior of the HR_{10} and $HRvar_{10}$ measures. The Fitbit PPG would be able to capture brief bursts in HR, as evidenced by a study in exercising awake individuals (Benedetto et al. 2018). Data with a ca. 1-s time resolution are only made available in the device's 'exercise' mode, which prevents sleep tracking. Fitbit may, nevertheless, still be able to detect variability changes over longer periods during sleep with a reasonable degree of accuracy even without providing users with high resolution or raw HR data (as seen in **Table 2.1**, where the ordering of the variance per sleep stage remains nearly intact between Fitbit and PSG).

Limitations

The missing information regarding an objective marker of "lights out" is a limitation of our study, which prevented us from estimating sleep latency. In addition, the number of measurements per minute provided by Fitbit varied, potentially due to variable signal quality and other internal decision-

making processes in Fitbit's proprietary data preprocessing algorithms. Updates to software or firmware could have occurred without notice, harboring a great potential to confound a research or clinical undertaking, particularly in longitudinal scenarios. Individual sleep episodes can vary appreciably even within an individual, and caution should be exercised when interpreting results from a Fitbit device. Not being able to blind participants from their own sleep data after its collection could influence their behavior in subsequent sleep episodes. This concern is particularly pressing when clinical or otherwise vulnerable populations are involved, and device output is interpreted which may impact treatment options or health outcomes. It is crucial that these devices be validated in more clinically diverse populations for this reason.

Conclusions

The use of multi-sensor wearable sleep trackers with inbuilt PPG technology in conjunction with accelerometer data, such as Fitbit Charge 2™, holds exciting opportunities to prospectively and accurately capture longitudinal rest-activity patterns with ecological validity. In validating Fitbit Charge 2™ against PSG conducted at home, we found unbiased mean estimates of various sleep and HR variables, although the data generally exhibited wide LoA, and we noticed problems in capturing the first REM sleep episode. The naturalistic design of the study increased the external validity and benefits our understanding of the performance of Fitbit Charge 2™ in a minimally controlled home environment. In addition, the cohort studied was more heterogeneous in terms of age and sex and comprised individuals who regularly perform shift work. The relatively large sample size favors our confidence in the conclusions we have drawn. Nevertheless, the use of the consumer-grade, wearable sleep tracker chosen was associated with various challenges, such as no access to raw data and receiving instead only preprocessed results from the proprietary algorithms. For the reliable use of consumer sleep technology for clinical and research purposes, access to raw data, the use of open-source data analysis algorithms, more control over the data flow to blind users and comply with all regulatory aspects are indispensable. Future validation studies of commercial devices should also be conducted in sleep disorder populations, such as narcolepsy, who often present with sleep onset REM sleep episodes that appear particularly difficult to detect.

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Conflict of Interests

None declared.

Diurnal variations in wearable-derived sleep characteristics in morning- and evening-type first responder shift workers: a naturalistic study

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(In preparation)

Abstract

First responders are exposed to circadian misalignment due to shift work and the need to maintain readiness for 24 hours a day. An individual's tolerance to shift work may be modulated by their chronotype and can be attributed to intrinsic variability in circadian and homeostatic characteristics. In this study, we therefore aimed to evaluate the potential of a consumer-grade rest-activity tracker to elucidate how differences in circadian and homeostatic characteristics of first responders of differing chronotypes affect rest-activity behavior, including sleep macrostructure, under naturalistic conditions. We monitored 89 individuals in the emergency medical rescue and law enforcement occupations of both sexes (54% females) and various ages (mean: 33.9 $\pm$ 7.7 years) around the clock for one month (32.5 $\pm$ 9.3 days) each with the Fitbit Charge 2^{TM} and assessed demographic and psychological variables. We collected a total of 2,974 individual sleep episodes scattered across 24 hours. In the monitored cohort, we found that sleep episodes formed approximately sinusoidal oscillations in waveshape across 24 hours, reflected in wearable-estimated sleep duration, wakefulness after sleep onset, REM sleep percentage in the first NREM-REM sleep cycle and REM sleep latency. Preferential Evening Types (reduced Horne-Östberg Morningness-Evening Questionnaire [rMEQ] score $\leq$ 14) organized their sleep differently than Preferential Morning Types (rMEQ > 14), showing longer sleep durations during the biological day. Phase position of sleep duration minimum was advanced 2.25 hours and REM sleep latency was 0.1 hours longer in morning types compared to evening types. These observations are consistent with findings from studies under stringently controlled laboratory conditions support the conclusion that a consumer-grade rest-activity tracker allows to estimate behavioral sleep/wake cycles and sleep macrostructure in shiftworkers under naturalistic conditions, consistent with their self-reported preferential chronotype.

Keywords: shift work, first responders, chronotype, circadian misalignment, wearables

Introduction

Frontline healthcare workers and law enforcement personnel often work around the clock in order to respond to emergency calls. Shift work forcefully disrupts an individual's natural rest-activity behavior, such that physical activity occurs during the biological night, whereas rest behaviors, such as sleep, occur during the biological day (Akerstedt 2003). Shift work may result in circadian misalignment, a state in which neither active nor rest behaviors can be performed at an optimal capacity during their respective dedicated intrinsic circadian windows of opportunity. Circadian misalignment may manifest itself in acutely apparent increases in sleepiness and impairments in waking cognitive performance (Chellappa et al. 2018), as well as reductions in sleep propensity, duration and consolidation (Czeisler et al. 1980b). In addition, a large variety of adverse health outcomes is associated with circadian misalignment (Sletten et al. 2020). Therefore, inexpensive and easy to use tools that reliably assess circadian misalignment under naturalistic conditions in sizeable vulnerable populations, such as medical and law enforcement personnel are urgently needed to treat and prevent adverse health outcomes related to shift work.

Chronotype describes the robust trait-like inter-individual differences in diurnal preferences in the management of rest-activity behavior on a continuum from 'morningness' to 'eveningness' (Horne and Östberg 1977). Chronotype can be determined conveniently and reliably with a variety of questionnaires, such as the self-report Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) (Horne and Ostberg 1976). The MEQ has been validated against intrinsic circadian rhythms of oral temperature (Horne et al. 1980; Horne and Östberg 1977), melatonin, cortisol and rectal temperature (Bailey and Heitkemper 2001; Duffy et al. 1999), and short-term (7-day) actigraphic rest-activity measurements (Thun et al. 2012).

It has long been theorized (Östberg 1973) that morning and evening chronotypes may tolerate circadian disruption due to shift work differently, and some experimental evidence indicates that restructuring of shift work schedules in accord with chronotype may actually benefit the health, sleep quality and psychological wellbeing of workers (Hittle and Gillespie 2018; Juda et al. 2013; Vetter et al. 2015). Tolerance of shift work can be defined as one's ability to adapt to shift work without suffering negative consequences (Andlauer et al. 1979). There is presently no consensus on which chronotype may be best suited for shift work, although there is limited evidence to suggest that evening activity preference may be related to enhanced shift work tolerance when compared to morning preference (Saksvik et al. 2011).

Seminal laboratory experiments under strictly controlled conditions have elucidated the organization of human sleep as a function of circadian phase (Czeisler et al. 1980a; Czeisler et al. 1980b; Zimmerman et al. 1980). When individuals were left to self-select episodes of bedrest and activity in an environment free of external time-cues such as the solar light-dark cycle, they developed free-running, non-24 hour bedrest-activity and core body temperature patterns characterized by bedrest-activity cycles period lengths of 20-28 hours. The number of times an individual elected to

initiate bedrest increased as core body temperature decreased, with bedrest number maximum occurring in phase with temperature minimum. At the temperature cycle maximum, proportion of REM sleep approached zero, whereas the opposite pattern was the case at the temperature minimum. Latencies to REM sleep were shortest just after occurrence of temperature minimum and longest near temperature maximum. Time asleep was longest at body temperature minimum and shortest at temperature maximum. Rectal temperature phase occurs approximately two hours earlier in morning types compared to evening types (Kerkhof and Van Dongen 1996), REM sleep is advanced and sleep latencies are longer during episodes of day sleep (Kerkhof and Lancel 1991).

This work aims to elucidate whether a consumer-grade wearable device such as Fibit Charge 2^{TM} would allow to document diurnal variations in sleep macrostructure under naturalistic conditions in first responders who perform shift work. We took advantage of their special working conditions to examine the occurrence of sleep at various clock times of the day and night. We expected to observe evidence of circadian misalignment manifest itself in fewer sleep episodes of shorter duration and greater disruption at unfavorable circadian phases compared to sleep episodes at favorable circadian phases. Furthermore, we aimed to characterize the organization of rest-activity behavior as a function of chronotype. Since there are individual differences in tolerance and adjustment to shift work attributable to variability in intrinsic circadian and homeostatic characteristics, we hypothesized that rest-activity patterns and the degree of circadian misalignment would vary as a function of chronotype. We expected to find a relative phase advance in macrostructural sleep variables regulated by the circadian clock in individuals with a morning activity preference compared to individuals with an evening activity preference. If supported by our data, these hypotheses would carry implications for rest-activity management for personnel in healthcare, law enforcement and other occupations characterized by shift work and prolonged on-call periods

Methods

We recruited a total of 89 individual emergency medical rescue workers (n = 61), police officers (n = 25) and emergency doctors (n = 3) of both sexes (females n = 48 [54 %]) and various ages (age: 33.85 $\pm$ 7.73 years) from urban locations in the greater Zurich area, Switzerland. Volunteers contributed to a larger study investigating sleep and resilience to psychological stress and trauma conducted from July 2017 through November 2019. They were recruited by informational media, as well as email and presentations at shift change. **Table 3.1** displays a selection of descriptive statistics of the study cohort's demographics. All participants provided written informed consent prior to participation, and the study protocol and all experimental procedures were approved by the Ethics Commission of the Canton of Zurich (KEK 2016-01357). All participants fulfilled inclusion criteria of an age between 18 - 65 years, body mass index (BMI) $\leq$ 25 (or if exceeding a BMI of 26, no presence of sleep problems, e.g., sleep breathing disorders, were reported), employment in one of two selected emergency rescue stations and one police station, possession of a smart phone and command of the German language.

Participants were excluded based on the presence of a neurological disorder diagnosis or head injury with potential to affect electroencephalographic (EEG) outcomes, reported consumption of > 5 alcoholic beverages / week or if a urine drug screen (Drug-Screen Multi 12-AE, Nal von Minden GmbH, Regensburg, DE) indicated drug abuse. All participants were shift workers and shift schedules differed between the professions. Emergency medical rescue workers (including emergency doctors) worked in cycles of two 12-hour day shifts followed by two 12-hour night shifts, interspersed with a day off, concluded by four days off, whereas police officers worked on four subsequent days with varying sleep and rest times, followed by two days off. Individual work schedules were not examined.

Experimental Protocol

The experimental protocol consisted of one month of continuous monitoring of wrist-derived rest-activity behavior including sleep, yielding 2,974 individual sleep episodes initiated at varying clock times throughout the day and night. We administered validated German versions of questionnaires to assess lifestyle, psychological variables, chronotype and sleep quality. Participants were paid CHF 50 for their participation and provided with an individualized sleep report based on their own data, which was explained to them by a study staff member at debriefing.

Morningness-Eveningness Questionnaire – A Reduced Scale

Chronotype was assessed by the Horne-Östberg Morningness-Eveningness Questionnaire – a Reduced Scale (rMEQ) (Adan and Almirall 1991). The rMEQ consists of five (items 1, 7, 10, 18 and 19) of the original 19 questionnaire items. It correlates strongly ($r = 0.92$, $p < 0.01$) with the original MEQ (Thun et al. 2012) with high reliability (Loureiro and Garcia-Marques 2015) and convergent validity (Adan and Almirall 1991; Caci et al. 2009; Chelminski et al. 2000). The rMEQ has been validated against actigraphy (Natale et al. 2006a; Thun et al. 2012) and skin temperature (Weidenauer et al. 2019) and was chosen over the original MEQ in this study in the interest of minimizing burden for participants. The rMEQ yields a range of scores forming five chronotype groups: Definitely Morning Type (22 – 25); Moderately Morning Type (18 – 21); Neither Type (12 - 17); Moderately Evening Type (8 – 11); and Definitely Evening Type (4 – 7) (Adan and Almirall 1991). In a data-driven approach, we divided our sample characterized by a bimodal rMEQ score distribution (**Figure 3.2**) into two groups, termed “Preferential Evening Type” ($n = 42$; MEQ ≤ 14) or “Preferential Morning Type” ($n = 43$; MEQ > 14). Subjective rMEQ-derived chronotype was corroborated by cluster analysis (Clark, Stucky et al., in preparation) of objective Fitbit-derived sleep timing data from 2,974 sleep episodes occurring at various clock times across the day and night for the study month. The rMEQ data from 4 study participants could not be included in our analysis due to incomplete data collection.

Pittsburg Sleep Quality Index (PSQI)

Individuals completed the Pittsburg Sleep Quality Index (PSQI) at the beginning of their study month and again at the end. Briefly, scores range from 0 to 21, with higher scores indicating worse sleep quality. A score above 5 indicates poor sleep quality (Buysse et al. 1989).

Wrist Activity Monitoring

A commercially available fitness tracker (Fitbit Charge 2™, Fitbit Inc., San Francisco, CA, USA), which records wrist activity by means of accelerometry and heart rate (HR) by means of photoplethysmography (PPG), was worn around-the-clock by all participants on their non-dominant wrist for one month (32.45 $\pm$ 9.29 days). A Fitbit proprietary algorithm which utilizes wrist-activity and PPG data outputs one of two types of sleep data per recorded sleep episode: (1) sleep "stages" data ("deep", "light", "REM" and "wake") with a granularity of 30 seconds or (2) sleep "classic" data ("sleep", "restless" and "wake") with a granularity of 60 seconds. The sleep "classic" data are generated instead of sleep "stages" data when battery charge is critically low, the sleep episode is less than 3 hours in duration or when contact to the PPG sensor is insufficient (Fitbit Inc. 2020b). The sleep recording sensitivity in the settings of the individual online Fitbit accounts of participants was set to "sensitive". Comparison with "normal" sensitivity revealed no impact on data output, when these two different setting options were verified. Sleep onset and offset times are generated by Fitbit per sleep episode.

Figure 3.1 Organization of rest-activity behavior including bedrest

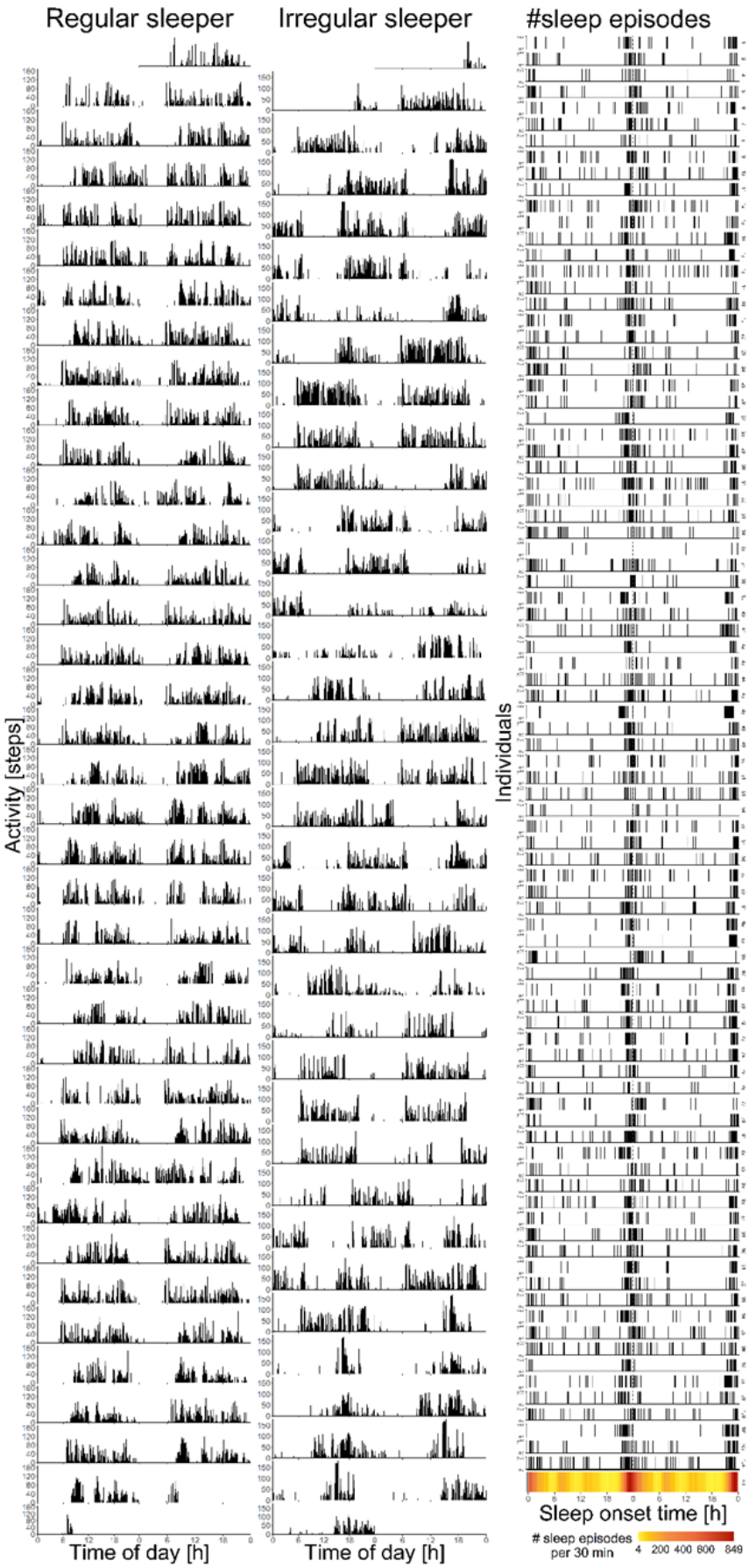

Figure 3.1. Organization of rest-activity behavior including bedrest. The left two columns display the double plotted raster actograms derived from Fitbit "steps" data over the course of the study month showing the rest-activity behavior of a "Regular sleeper" (left) and an "Irregular sleeper" (middle). Amplitude (number of "steps" per minute) is plotted on the vertical axis, whereas "Time of day" in hours is plotted on the horizontal axis. The right-most panel ("#sleep episodes") displays the timing of habitual sleep occurring at multiple clock times of the day and night derived from Fitbit sleep onset times in a double plotted raster format for all participants (n = 89). The vertical axis displays all individuals' data sets, whereas the horizontal axis displays "Sleep onset time" in hours. The number of sleep episodes per 30 minutes is displayed beneath and is color-coded to highlight density of sleep onset occurrence.

In a subsample of 61 individuals, we polysomnographically recorded nocturnal sleep during two nights at home while simultaneously wearing the Fitbit Charge 2™, permitting its validation against the gold standard of polysomnography (Stucky et al. 2020).

Statistical Analysis

Group comparisons of demographic data by chronotype were performed using *R* (version 4.0.0) and SAS (version 9.4, Cary, NC, USA). For all analysis no involving Fitbit data, the Mann-Whitney *U* Test / Wilcoxon (PROC NPAR1WAY) was applied to continuous data, whereas Fisher's Exact Test (PROC FREQ) was applied to frequency data. Associations between continuous demographic data were tested with Spearman's Rank-Order correlation coefficient (PROC CORR). An α of $p < 0.05$ was considered statistically significant.

All statistical analyses of Fitbit data were carried out in the statistical programming environment *R* (version 4.0.0). The diurnal analyses were conducted using the *mgcv* package (version 1.8-31). Non-linear diurnal modulations over time of day and the repeatedly measured sleep episodes per individual suggested the use of generalized additive mixed models (GAMMs). We used suitable distribution families and link functions to model individuals' diurnal modulations over time. In particular, the non-symmetrically distributed Gamma family was applied to REM sleep percentage in first NREM-REM sleep cycle, REM sleep latency and wakefulness after sleep onset (WASO). For sleep duration, the Gaussian family with a log link function was selected. Only for WASO were the residual assumptions only partially fulfilled. This is due to the bimodal nature of the distribution of WASO, which might originate from an uncorrected or unknown factor or from the way Fitbit's algorithm operates.

We calculated the confidence intervals of diurnal data via posterior simulation on the model with 100,000 random samples, which can be done with the *simulate* function in the *gratia* package of *R* (version 0.4.1). Here, skewedness is computed as the difference in slopes between the midpoints of the maximum to minimum and minimum to maximum. The computed confidence intervals are simultaneous, as mentioned in Ruppert and colleagues (2003). Therefore, these intervals can effectively overcome the multiple testing issue in a continuous fashion. Our code for computing the reported confidence intervals is a version of the *confint* function in *gratia.* The gratia::confit function calculates simultaneous confidence intervals for the first derivatives of a fitted generalized additive model and not for the differences between two groups, nor does it provide simultaneous intervals for

the fitted curves. We thus modified the code slightly to sample differences between the fitted curves of the two chronotypes as well as sampling the fitted curves themselves, instead of the first derivatives. We corrected all models with linear terms for sex and age. The smooth term per sleep onset time and chronotype is a cyclic cubic regression spline with knots at hour 0 and 24 to ensure a continuous transition around midnight. We limited the smooth terms to 7 degrees of freedom to avoid overfitting. The plots always display the model estimate for a female with age 23 years, the minimum age in the whole sample.

We computed the variables REM sleep percentage in the first NREM-REM sleep cycle (REM%) and REM sleep latency (RL) in accordance with criteria as delineated in Feinberg and Floyd (1979). For WASO, we took sleep onset and offset times from Fitbit, except when the first stage after sleep onset or the last stage before sleep offset was labelled as "wake", which is a peculiarity of the Fitbit algorithm that sometimes occurs. In the latter case, we omitted these short wake episodes and adjusted the sleep onset and offset times accordingly. We only included the fine-grained "stages" data to the REM sleep calculations. For WASO, we considered both the "stages" and "classic" data, such that we combined the "classic" data variable "restless" with "wake", in accordance with prevailing Fitbit guidelines (Fitbit Inc. 2020b). Finally, we computed the RL decile density plot with bootstrapped confidence intervals using 1,000 bootstrap samples and multiple testing correction as described in Rousselet and colleagues (2017) and implemented in the *rogme* package (version 0.2.1).

Results

Distribution of rest-activity behavior

On average, most individuals tended to prefer to initiate sleep between the hours of about 21:00 – 02:00 h, although there is considerable variability in sleep timing between individuals. **Figure 3.1** shows Fitbit 'steps' illustrating the rest-activity behavior in two representative participants across the entire recording period. Whereas there is a pattern of rest activity behavior that is relatively uniform and occurring at regular intervals in the "Regular sleeper" (**Figure 3.1**), the rest-activity behavior of the "Irregular sleeper" is in contrast erratic, with periods of sleep and wakefulness less rhythmically patterned over the course of the one month study period. The "Regular sleeper" was female, 42 years of age with a BMI of 26, a "Moderately Morning Type" (rMEQ score = 19), drank alcohol "occasionally", was a non-smoker, and was an emergency medical rescue worker engaged in full time shift work with 25 years of experience on the job and in shift work, respectively. The "Irregular sleeper" was male, 34 years of age with a BMI of 25, a "Neither Type" (rMEQ score = 12), drank alcohol "weekly", smoked "occasionally", and was also a full time emergency medical rescue worker performing shift work He was on duty in a different rescue station and had considerably less experience both in his profession and with shift work, as he indicated just less than seven years of experience in both. The PSQI scores of both the "Regular sleeper" and "Irregular sleeper" indicated good sleep (PSQI scores ≤ 5) when surveyed at both the start and end of their study months.

Distribution of chronotypes

Our study cohort of 85 individuals was comprised of 1 (1.12%) Definitely Morning Type, 19 (22.35%) Moderately Morning Types, 45 (52.94%) Neither Types and 20 (23.52%) Moderately Evening Types. There were no Definitely Evening Types in our sample. Based on the bimodal distribution of the rMEQ scores (**Figure 3.2**), we stratified the sample in a data-driven fashion into two chronotype groups of Preferential Evening Type and Preferential Morning Type with a median split. We found that the Preferential Evening Type group was made up of 22 (52.38%) Neither Types and 20 (47.62%) Moderately Evening Types, whereas the Preferential Morning Type group was made up of 1 (2.33%) Definitely Morning Type, 19 (44.19%) Moderately Morning Types and 23 (53.49%) Neither Types.

Figure 3.2 Distribution of morningness-eveningness scores

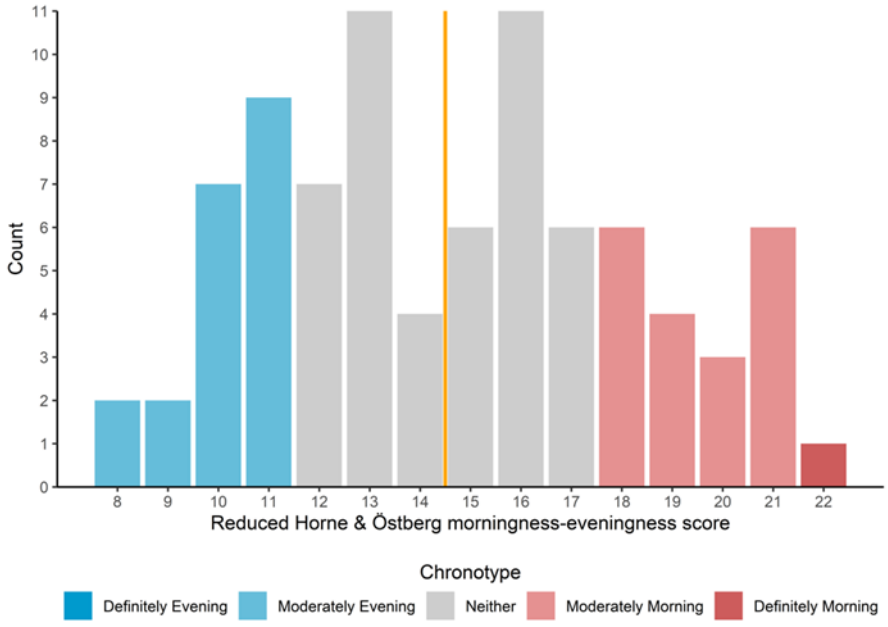

Figure 3.2. Distribution of morningness – eveningness scores (n = 85) derived from the Horne-Östberg Morningness-Eveningness Questionnaire – A Reduced Scale (rMEQ) (Adan and Almirall 1991). The rMEQ scores are plotted on the horizontal axis and their colors correspond to the rMEQ chronotypes labeled beneath. The number ("Count") of individuals per score is plotted on the vertical axis. The orange vertical line delineates the Preferential Evening Types (rMEQ score $\leq$ 14; n = 42) and Preferential Morning Types (rMEQ score > 14; n = 43).

A summary of selected demographic outcomes is presented in **Table 3.1.** Preferential Morning Types were on average 5.5 years older than Preferential Evening Types. Age weakly correlated with rMEQ score, such that rMEQ score became higher (indicating increasing morningness) as age increased (r_s = 0.35, $p < 0.001$). The two groups did not differ with respect to sex, BMI, and frequency of beverages consumed containing alcohol or caffeine. A trend-wise difference was observed with respect to smoking frequency (p = 0.07) and number of days per week engaging in physical fitness activities (p =

0.07), indicating that Preferential Evening Types may smoke more and exercise less frequently than Preferential Morning Types. The distribution of emergency medical rescue workers (including emergency doctors) and police officers did not differ between Preferential Evening Types and Preferential Morning Types. Preferential Evening Types and Preferential Morning Types did not differ with respect to years of experience in their current profession nor with years of experience performing shift work, respectively. Most shift work experience in our sample appears to have been garnered from the current profession, since these two variables correlate strongly ($n = 78$; $r_s = 0.71$, $p < 0.0001$). Subjective sleep quality (measured by the PSQI), posttraumatic stress (PCL-5), and perceived stress (PSS-10) assessed at the start and end of the study month did not differ between Preferential Evening Types ($n = 38$) and Preferential Morning Types ($n = 43$).

Table 3.1 Demographic characteristics

Variable	Frequency	Total Sample Size	Preferential Morning Type	Preferential Evening Type	*p*
Sample size (*n*)		89	43	42	
Age (y)		33.85 ± 7.73	36.72 ± 9.24	31.26 ± 4.86	0.0053
Sex (*n* female; male)		48; 41	20; 23	25; 17	0.3249
BMI		23.88 ± 3.02	24.2 ± 2.99	23.69 ± 3.09	0.2934
Profession (*n* police; paramedic)		25; 64	13; 30	12; 30	1.0000
Experience in profession (y)		9.00 ± 7.01	10.81 ± 8.02	7.48 ± 5.65	0.1000
Experience in shift work (y)		10.92 ± 7.20	12.83 ± 8.59	9.38 ± 5.28	0.1000
Smoking frequency (*n*)	Daily	8	1	7	0.0727
	Occasionally	13	6	6	
	Never	68	36	29	
Alcohol frequency (*n*)	Daily	8	4	4	0.7255
	Weekly	52	27	23	
	Occasionally	29	12	15	
	Never	0	0	0	
Caffeine frequency (*n*)	≥ 5 days/week	58	29	28	0.4941
	1 - 4 times/week	25	13	10	
	<1/week	4	1	3	
	Never	2	0	1	
Sports frequency (*n*)	≥ 5 days	6	4	2	0.0719
	4 days/week	10	8	2	
	3 days/week	26	9	16	
	2 days/week	31	17	11	
	1 day/week	11	4	7	
	0 days/week	5	1	4	
Alcohol (*n* drinks/week)		1.57 ± 1.24	1.51 ± 1.13	1.6 ± 1.4	0.8863
Caffeine (*n* drinks/day)		2.62 ± 2.12	3.05 ± 2.29	2.32 ± 1.93	0.1080
rMEQ		14.66 ± 3.59	17.67 ± 2.1	11.57 ± 1.61	0.0000
PSQI (start of study month)		5.73 ± 2.69	5.44 ± 2.93	6.05 ± 2.4	0.2153
PSQI (end of study month)		6.24 ± 2.34	6.23 ± 2.41	6.29 ± 2.37	0.8038
PCL-5 (start of study month)		6.97 ± 8.97	8.53 ± 10.73	5.83 ± 6.94	0.2073
PCL-5 (end of study month)		5.52 ± 7.74	5.21 ± 7.62	5.80 ± 8.07	0.9707
PSS-10 (start of study month)		12.03 ± 5.02	12.07 ± 5.26	12.07 ± 5.02	0.9438
PSS-10 (end of study month)		10.07 ± 4.68	9.37 ± 4.36	10.93 ± 5.12	0.2451

Values indicate mean + standard deviation. The p-values reflect comparison of chronotype groups. Frequency data tested via χ^2 (i.e., sex, profession, smoking-, alcohol-, caffeine-, and sports frequency); otherwise Mann-Whitney U Test was performed. Total sample size equals 89 individuals, whereas Preferential Morning and Evening Types = 43 and 42 (i.e., 85) individuals, due to missing rMEQ questionnaire scores from 4 individuals. PSQI = Pittsburgh Sleep Quality Index; PCL-5 = Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; PSS-10 = Perceived Stress Scale-10. For variables PCL-5 (study end): $n_{\text{Preferential Evening Types}} = 40$. For PSS-10 (study start): $n_{\text{Preferential Evening Types}} = 40$. For variables "Experience in profession" and "Experience in shift work": $n_{\text{Preferential Morning Types}} = 40$ and $n_{\text{Preferential Evening Types}} = 39$, due to attrition.

Wrist activity-derived sleep outcomes

The occurrence of sleep across the day was not random. We observed approximate diurnal oscillations in the pattern of sleep duration, WASO, REM% and RL as a function of sleep onset time, as evident from the difference from intercept at many clock times and the occurrence of amplitude maxima and minima. The duration of sleep episodes was typically greatest when sleep was initiated during the night, reaching a maximum mean duration of 8.57 (95% confidence intervals: 8.24, 8.94) hours at 22:26:24 (22:16:19, 22:39:22) and lowest when initiated during the day, with a minimum mean duration of 2.23 (1.94, 2.56) hours at 14:55:41 (14:12:29, 15:23:02) (**Figure 3.3**). We observed a significant effect of factor "age" for sleep duration ($p < 0.01$), such that as age increased sleep duration decreased. The effect of "age" remained significant ($p < 0.05$) in the model when the factor "chronotype" was included. The variable WASO revealed the approximate inverse waveshape to that of sleep duration, such that the maximum mean percentage of 40.18% (34.47%, 45.98%) was observed at 16:06:14 (15:38:53, 16:22:05), whereas the minimum mean percentage of 14.24% (11.62%, 16.73%) occurred at 23:35:31 (23:02:24, 23:54:14).

Figure 3.3 in the occurrence and internal organization of sleep across the day derived from Fitbit

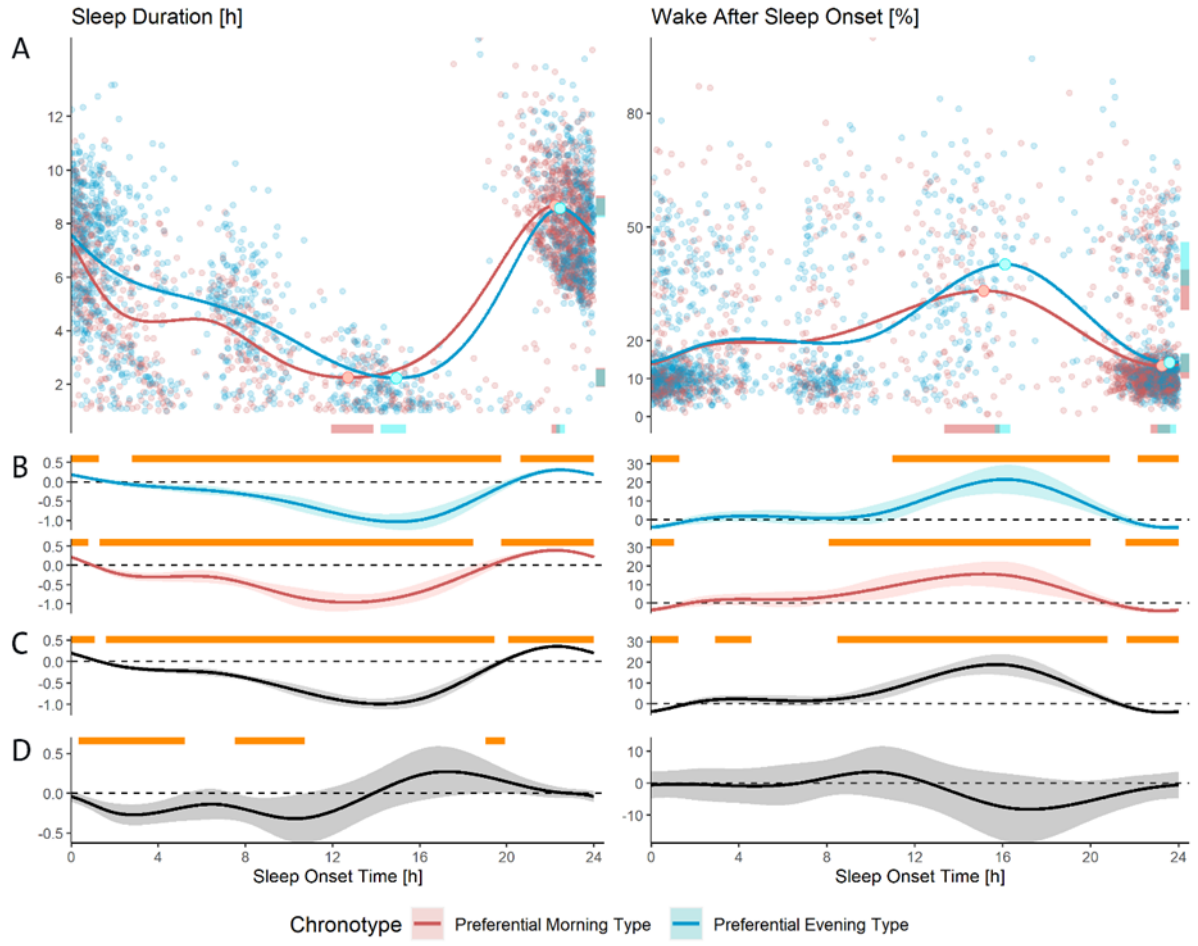

Figure 3.3. Variations in the occurrence and internal organization of sleep across the day derived from Fitbit sleep data. Preferential Morning Type (n = 43; red dots and lines) and Preferential Evening Type (n = 42; blue dots and lines) data are

plotted for variables 'Sleep Duration' (left) and 'Wake After Sleep Onset' (right). All plots have time of sleep onset in hours as the horizontal axis. Panel A displays individual data points, their averages (curves) as well as peak and nadir (circles on curves). The vertical axis of 'Sleep Duration' displays time in hours, whereas this axis shows percentage of sleep episode for variable 'Wake After Sleep Onset'. Confidence intervals are displayed (bar shapes color-coded to match the respective chronotype) and are displayed horizontally beneath and vertically to the right of the figures of panel A. Panels B, C and D display non-linear diurnal modulations over time of day and 95% confidence intervals (shaded area around curves); the vertical axes are in arbitrary units; orange bars of panels B and C indicate that values differ significantly from intercept (dashed line). Panel B displays data per chronotype, whereas panel C shows data for the entire sample. Panel D shows the difference between the chronotypes and orange bars indicate where their waveshapes differ significantly from one another.

The maximum mean REM% of 21.57% (19.17%, 24.29%) occurred at 08:55:41 (06:44:38, 10:01:55) whereas the minimum mean of 12.91% (9.90%, 15.58%) occurred at 19:40:48 (18:47:31, 21:18:43) (**Figure 3.4**). The time until onset of REM sleep varied in the approximate inverse pattern to that of REM%, such that the shortest latencies were observed during the morning hours, whereas the longest latencies occurred during the evening and nighttime hours. We found the mean minimum of RL of 1.42 (1.23, 1.58) hours to occur at 08:02:24 (04:53:46, 10:49:26), whereas the mean maximum of 1.72 (1.54, 1.94) hours occurred at 19:53:46 (18:10:05, 00:08:38).

Figure 3.4 Variations in the occurrence and internal organization of REM sleep across the day derived from Fitbit

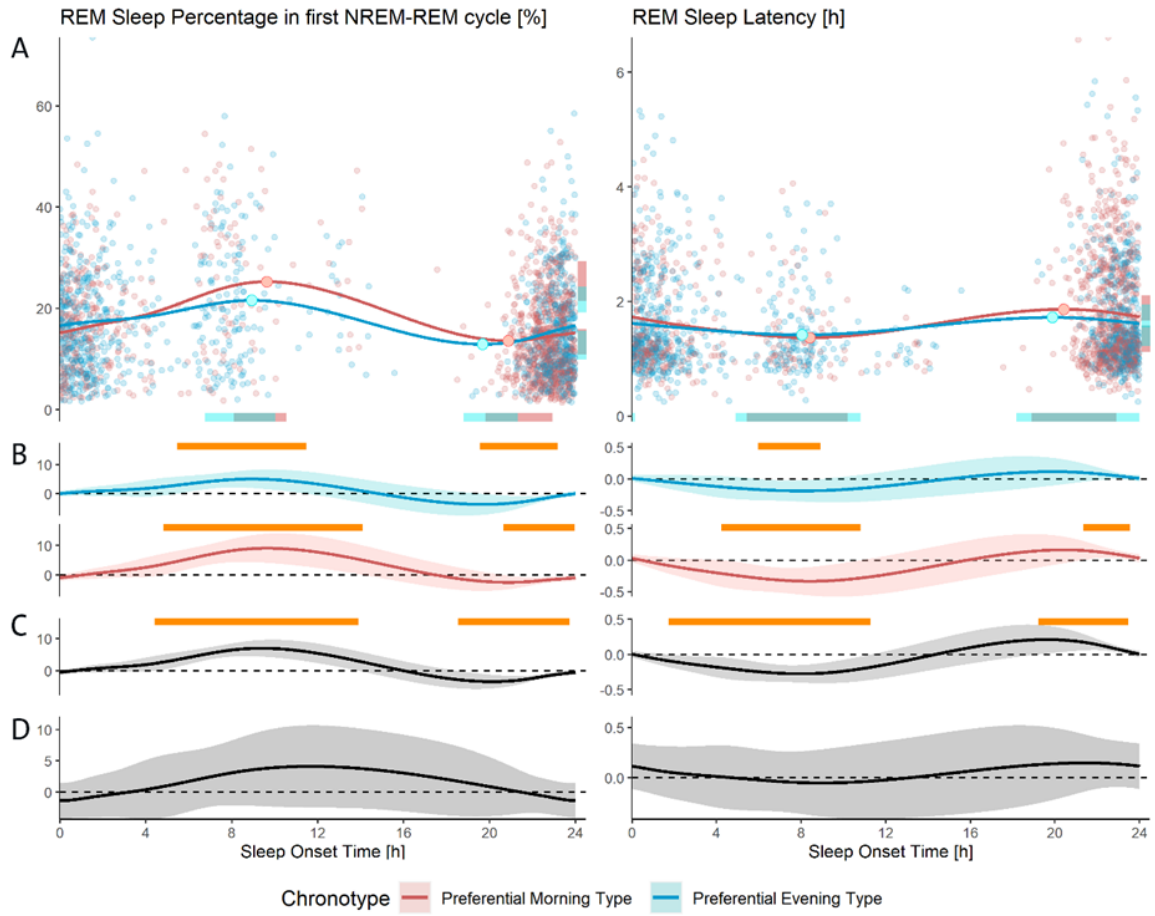

Figure 3.4. Variations in the occurrence and internal organization of REM sleep across the day derived from Fitbit sleep data. Preferential Morning Type (n = 43; red dots and lines) and Preferential Evening Type (n = 42; blue dots and lines) data are plotted for variables 'REM Sleep Percentage in first NREM-REM cycle' (REM%; left) and 'REM Sleep Latency' (RL; right). All plots have time of sleep onset in hours as the horizontal axis. Panel A displays individual data points, their averages (curves) as well as peak and nadir (circles on curves). The vertical axis of 'REM%' displays time as a percentage of sleep episode, whereas for variable 'RL' the vertical axis shows time in hours. Confidence intervals are displayed (bar shapes color-coded to match the respective chronotype) and are displayed horizontally beneath and vertically to the right of the figures of panel A. Panels B, C and D display non-linear diurnal modulations over time of day and confidence intervals (shaded area around curves); the vertical axes are in arbitrary units; orange bars of panels B and C indicate that values differ significantly from intercept (dashed line). Panel B displays data per chronotype, whereas panel C shows data for the entire sample. Panel D shows the difference between the chronotypes.

Wrist activity-derived sleep outcomes and chronotype

Chronotype preference influenced the phase of mean sleep duration minimum, such that Preferential Morning Types achieved a mean minimum of 2.25 (1.91, 2.60) hours at 12:43:12 (11:57:07, 13:52:19) compared to Preferential Evening Types, who reached a mean minimum of 2.23 (1.92, 2.56) hours at 14:55:41 (14:12:29, 15:23:02), representing an advance of 2.21 hours. The chronotypes distributed the duration of their sleep episodes differently across the day as a function of sleep onset time, such that compared to Preferential Morning Types, Preferential Evening Types showed, on average, sleep episodes of significantly greater duration when sleep was initiated between 00:20:10 and 05:12:29 (+1.13 h), between 07:30:43 and 10:43:41 (+0.94 h) but not between 19:01:55 and 19:55:12 (-1.02 h) (**Figure 3.3, panel D**). The phase of mean sleep duration maximum, as well as the diurnal variation in mean WASO, REM% and RL did not differ between the two groups. Nevertheless, the shape of the distribution of REM sleep latency differed between the chronotypes, such that RL was on average delayed approximately 0.1 hours in Preferential Morning Types compared to Preferential Evening Types, reflected by greater weight in the distribution that is driven by more frequent outliers or increased first REM sleep episodes (**Figure 3.5)**.

Figure 3.5 Density distribution of REM sleep latency

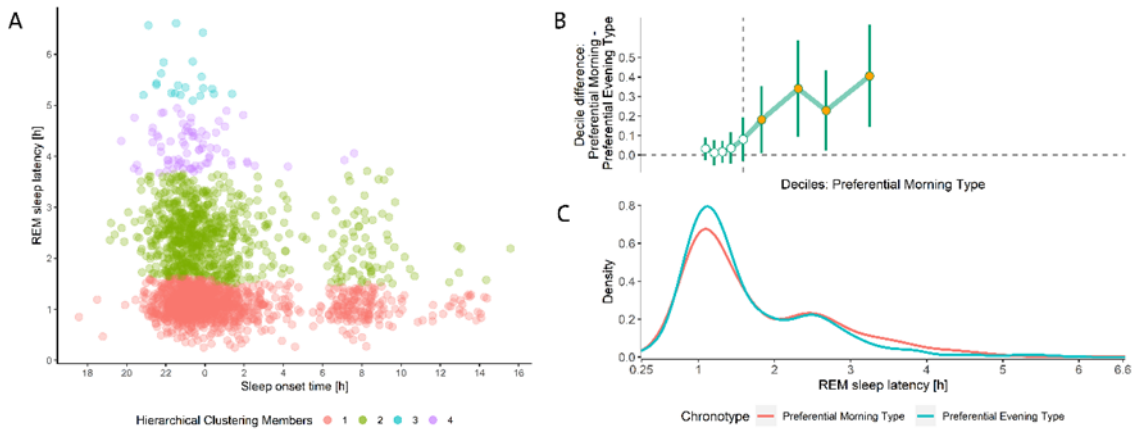

Figure 3.5. Density distribution of REM sleep latency (RL). Panel A displays hierarchical clustering of all RL data points in a color-coded manner in all participants (n = 89). The horizontal axis shows sleep onset time in hours, whereas the vertical axis shows RL in hours. Panel B displays the decile difference between Preferential Morning Type (n = 43) and Preferential Evening Type (n = 42). Circles represent deciles, whereas whiskers show bootstrapped confidence intervals corrected for multiple comparison. The dashed vertical line is the median of Preferential Morning Types. The horizontal axis shows RL in hours, whereas the vertical axis shows density. Panel C shows the distribution of RL times by chronotype, whereby Preferential

Morning Types are shown in red and Preferential Evening Types are shown in blue. Panel C shares the horizontal axis with Panel B; the vertical axis is density.

Discussion

In this study, we aimed to investigate the utility of a consumer-grade wearable fitness tracker (Fitbit Charge 2^{TM}) to capture rest-activity patterns and sleep macrostructure in shift worker populations of emergency medical rescue workers and law enforcement personnel longitudinally under naturalistic conditions. Based on nearly 3,000 sleep episodes initiated at clock times across the day and night, we demonstrated that it is feasible to reliably capture rest-activity data including sleep macrostructure with a commercially-available wearable fitness tracker, which produced results similar to what would be expected with polysomnography in a shiftwork population.

Consistent with our hypothesis, we observed fewer sleep episodes and of shorter duration at unfavorable phase positions and these sleep episodes were characterized by greater disruption compared to sleep initiated at favorable phase positions. More specifically, 40.25% (1,197) of all sleep episodes was initiated by individuals irrespective of chronotype between 22:00 and 24:00, whereas only 1% (30 episodes) was initiated between 18:00 and 20:00. Sleep episodes of the greatest duration (ca. 8 hours) were initiated between 20:00 and 22:00, whereas the shortest sleep durations (ca. 2 hours) were initiated between 16:00 and 18:00. Sleep was most disrupted between 16:00 and 18:00 and least disrupted between 22:00 and 02:00, reflected in the highest (ca. 40%) and lowest (ca. 14%) proportions of WASO observed in these respective time periods. These findings correspond closely to what models of the wake maintenance zone evoked by oscillatory processes of the endogenous circadian pacemaker and homeostatic regulation of sleep propensity would predict (Lavie 1986; Strogatz et al. 1987).

When bedrest occurs on the ascending slope of the core body temperature rhythm, then sleep propensity is low and sleep continuity is severely disrupted (Dijk and Czeisler 1994). From the data reported here it is not possible to make any direct inferences about intrinsic circadian core body temperature rhythms because these data were not collected. We captured the proportion of REM sleep during the first NREM-REM sleep cycle and latencies to the first REM sleep episode to estimate the timing of REM sleep that is coupled tightly to the core body temperature rhythm (Czeisler et al. 1980b). The REM% was not randomly distributed in our sample but rather approximated a diurnal oscillatory pattern, such that proportions were highest between 08:00 and 10:00 and lowest between 18:00 and 22:00. Latencies to REM sleep onset were shortest (ca. 1 hour 45 minutes) during morning hours of 06:00 to 08:00 and longest (ca. 2 hours) during the evening and nighttime hours of 20:00 to 22:00. These curves show the expected approximate inverse relationship and align closely with curves reported in the literature with respect to REM sleep diurnal timing under imposed ultradian activity-bedrest conditions (Czeisler et al. 1980b). Sleep propensity and sleep duration were lowest and WASO percentage was highest on the ascending slope of the REM% curve in our sample, whereas the exact opposite pattern emerged on the descending slope. These findings indicate entrainment in the

underlying intrinsic circadian rhythms to environmental *Zeitgebers* and suggest misalignment of the endogenous circadian rhythms to the behavioral cycles. In other words, waking and sleep episodes occurred frequently out of phase with intrinsic circadian rhythms.

Preferential Morning Types attained their sleep duration minimum earlier than Preferential Evening Types. This finding indicates that the prolonged (~ 30 days and nights) estimation of sleep-wake patterns with a commercially available activity tracker can be useful to estimate the circadian phase of sleep propensity in shift workers under naturalistic conditions. Although no difference was evident in the phase positions of the sleep duration and WASO maxima, preferential evening types slept appreciably longer than preferential morning types during sleep episodes initiated in nighttime and morning (+ 2.1 h) but not evening (- 1.0 h) hours. More specifically, Preferential Evening Types seemed to scavenge sleep whenever their occupational demands, social opportunities and intrinsic circadian and homeostatic processes permitted. Preferential Morning Types, in contrast, tended to consolidate their bedrest and sleep more at nighttime and less during the daytime. This could be cautiously interpreted as in indication that Preferential Evening Types in our sample cope differently with the demands of shift work and behave in a more adaptive manner, potentially indicating a more flexible circadian sleep-wake regulation. An attendant and not mutually exclusive interpretation might be that the occurrence of sleep episodes of greater duration throughout the daytime could suggest higher homeostatic sleep pressure in Preferential Evening Types compared to Preferential Morning Types, the latter of which are able to obtain the sleep they require in episodes clustered around conventional sleeping times at night. Electroencephalographic recordings indicate that sleep homeostasis dissipates and accumulates faster during sleep and wakefulness in some individuals with morning preference when compared to individuals with an evening preference (Mongrain et al. 2006). Accelerated dissipation and accumulation of homeostatic sleep propensity in some individuals with morning activity preference would fit the pattern of reduced sleep duration during daytime and may also be consistent with the higher proportion of prolonged REM sleep latencies (**Figure 3.5**) in preferential morning type individuals. Nevertheless, the differences reported here need to be interpreted with caution because the two preferential chronotype groups differed in age. A previous study conducted under controlled laboratory conditions reported reduced mean daytime sleep propensity and shorter daytime sleep durations in older adults (> 60 years) when compared to younger adults (~ 22 years) (Klerman and Dijk 2008). Because individuals in the Preferential Morning Types group (~ 36.7 years) were only 5.5 years older than those of the Preferential Evening Types group (~ 31.3 years) and only five individuals were above age 50, a pronounced effect of advanced age on daytime sleep propensity was predictably absent and incorporated in the statistical analyses.
We did not observe phase position differences for REM% and RL maxima or minima between the preferential chronotype groups. The estimated amplitudes of the diurnal variation in these REM sleep variables were smaller and the estimation of maxima and minima less reliable than for sleep duration and WASO. This may be due to the relatively low number of observations at the phase position of the

estimated maxima and minima of these particular variables (~ 18:00-22.00). The relative absence of observations at these particular locations is likely due to the influence of the wake maintenance zone (Dijk and Czeisler 1994), although social pressures cannot be ruled out. Despite the difference in the mean rMEQ scores between the preferential morning and evening type groups, both groups included roughly 50% individuals without clear chronotype. This overlap may have obscured subtle differences between the two groups. Alternatively, the proprietary sleep-scoring algorithm may have been uncertain in reliably recognizing REM sleep. The Fitbit Charge 2™ is not a precision scientific research instrument and may not be able to discriminate between the different substates of sleep, although previous research in the laboratory indicates that this device is particularly promising in estimating REM sleep (de Zambotti et al. 2017). The hierarchical clustering and density distribution of the REM sleep latencies (**Figure 3.5**) suggests a high proportion of missed REM sleep episodes. Validation studies against polysomnography at different circadian phases are needed to evaluate whether Fitbit Charge 2™ is reliable and accurate in quantifying diurnal REM sleep characteristics under natural conditions.

Some limitations of the current study also need to be mentioned. The rMEQ is not a shiftwork-specific instrument, and thus may have been vulnerable to error when individual shift workers in our sample attempted to reflect on their own habits and preferences to answer questions originally designed to address non-shiftwork populations. The absence of data on the individual work and rest schedules of the study participants represents another weakness. There is evidence that different work schedule features favor adjustment in a chronotype-dependent manner (e.g., forward rotation may benefit evening types) (Folkard and Hunt 2000) and data which would locate work days and free days during the study month would be relevant to distinguish between rest-activity behavior elicited by occupational requirements or by individual and more biologically driven processes. We did not distinguish between main sleep episodes and naps in this report and do not have a means of discerning them with high accuracy. For instance, it is not known whether a sleep episode of less than 7-8 hours was a nap and deliberately short or an unsuccessful attempt at a main sleep episode. Finally, we are limited to cautious, probabilistic statements about variation in patterns of intrinsic circadian and homeostatic processes and their influences due to the presence of masking factors such as light exposure, time cues, meals, occupational obligations, social opportunities, and intake of psychoactive substances such as caffeine and alcohol. All these factors could have magnified variability in the data and reduced the signal-to-noise ratio yet are common under naturalistic conditions.

On the other hand, the collection of rest-activity behavior continuously and around-the-clock over one month in a naturalistic environment yields valuable illuminating data. The prospective design and naturalistic conditions boost the external validity of our findings that are typically lacking in cross-sectional epidemiological studies and controlled laboratory experiments. The prospective investigation of shift workers under naturalistic conditions performed here provides further evidence which suggests that the behavioral and intrinsic circadian rhythms of individuals performing shiftwork are chronically

misaligned. Our findings suggest that misalignment caused by shiftwork may be modulated by chronotype. Ongoing further analyses of the present data aim to investigate whether there are reliable and systematic differences in heart rate and heart rate variability estimates during sleep between morning- and evening-type first responders under naturalistic conditions. Research with wearable devices should continue to attempt building a bridge between epidemiological studies and laboratory experiments with objective estimates of the prevalence of cardiovascular, metabolic, endocrine and other disease states in at-risk populations such as first responder shift workers.

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Effects of shift work-related circadian misalignment and chronotype on diurnal cardiac autonomic patterns in police and emergency rescue workers under naturalistic Conditions

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(In preparation)

Abstract

First responders are exposed to circadian misalignment due to shift work and the need to maintain readiness for 24 hours a day. An individual's tolerance to shift work may be modulated by their chronotype and can be attributed to intrinsic variability in circadian and homeostatic characteristics. In this study, we therefore aimed to evaluate the potential of a consumer-grade rest-activity tracker to elucidate how differences in circadian and homeostatic characteristics of first responders of differing chronotypes affect rest-activity behavior, including sleep macrostructure, under naturalistic conditions. We monitored 89 individual paramedics (n = 61), police officers (n = 25) and emergency doctors (n = 3) of both sexes (54% females) and various ages (mean: 33.9 $\pm$ 7.7 years) around the clock for one month (32.5 $\pm$ 9.3 days) each with the Fitbit Charge 2™ and assessed demographic and psychological variables. We collected a total of 2,974 individual sleep episodes scattered across 24 hours. In the monitored cohort, we found that sleep episodes formed approximately sinusoidal oscillations in waveshape across 24 hours, reflected in wearable-estimated sleep duration, wakefulness after sleep onset, REM sleep percentage in the first NREM-REM sleep cycle and REM sleep latency. Preferential Evening Types (reduced Horne-Östberg Morningness-Evening Questionnaire [rMEQ] score $\leq$ 14) organized their sleep differently than Preferential Morning Types (rMEQ > 14), showing longer sleep durations during the biological day. Phase position of sleep duration minimum was advanced 2.25 hours and REM sleep latency was 0.1 h longer in morning types compared to evening types. These observations consistent with findings from studies under stringently controlled laboratory conditions support the conclusion that a consumer-grade rest-activity tracker allows to estimate behavioral sleep/wake cycles and sleep macrostructure in shiftworkers under naturalistic conditions, consistent with their self-reported preferential chronotype. If supported by our data, these hypotheses would carry implications for rest-activity management for personnel at the healthcare and law enforcement frontline

Keywords: shift work, first responders, chronotype, cardiaovascular, sleep, circadian misalignment, wearables

Introduction

The intrinsic circadian system and sleep-wake behavior each independently influence autonomic nervous system functions and require synchronization to ensure optimal performance and health (Trinder et al. 2012). Circadian misalignment describes the condition of disruption between the intrinsic circadian rhythm and behavioral sleep-wake cycles, such that they are no longer functioning in a synchronized manner. When occurring chronically, as is frequently the case among shift workers, circadian misalignment is associated with an increased risk for various clinically relevant disease states and adverse health outcomes (Sletten et al. 2020), including cardiometabolic disease and adverse cardiovascular events such as myocardial infarction, stroke, and ventricular arrhythmias (Chellappa et al. 2019; Rüger and Scheer 2009; Vyas et al. 2012).

Not all individuals performing shift work are equally vulnerable to the adverse health effects of circadian misalignment. A large study in > 430'000 adults revealed increased mortality and levels of cardiometabolic risk factors in individuals with later chronotype (i.e., evening preference for daytime activities and later bed- and waketimes) when compared to individuals with earlier chronotypes (i.e., morning preference) (Knutson & von Schantz, 2018). The increased mortality and cardiovascular morbidity were tentatively attributed to more pronounced chronic circadian misalignment in evening chronotypes when compared to morning chronotypes. We recently recorded under naturalistic conditions across one month, the rest-activity patterns and estimated sleep macrostructure in emergency medical rescue workers and law enforcement personnel performing shift work. We employed the multisensory wrist-band Fitbit Charge 2^{TM} that combines the recording of movements and heart rate patterns, to track sleep-wake states with reasonable accuracy when compared to gold-standard polysomnographic recordings (De Zambotti et al., 2018; Stucky, Clark et al., submitted). Based on nearly 3'000 Fitbit estimated sleep episodes initiated at clock times across day and night, we found evidence that the intrinsic circadian rhythms and sleep-wake behavior of this shift work population are indeed frequently misaligned. Furthermore, sleep-wake behavior was modulated by chronotype, such that the phase position of the minimum sleep length was delayed by ~ 2.2 hours in preferential evening types when compared to preferential morning types (Clark, Stucky et al., submitted). The longitudinal sleep-wake tracking further suggested that the preferential evening types initiated their sleep episodes whenever their occupational demands, social opportunities and intrinsic circadian and homeostatic processes permitted, whereas the preferential morning types tended to consolidate their bedrest and sleep more at nighttime and less during the daytime. Because cardiac-autonomic outcomes are not governed exclusively by the circadian system but are at least partially sleep-wake dependent (Burgess et al. 1997; Viola et al. 2002), we aimed to investigate in our sample whether heart rate (HR) and heart rate variability (HRV) as measured as the variance of HR (HRvar) differ between preferred evening- and morning-type first responders performing. These two measures provide reliable physiological markers of cardiovascular health and are predictors of future health problems and all-cause mortality (Shaffer et al. 2014).

Composite phase deviation (CPD) is a newly proposed means of mathematically quantifying the irregularity of behavioral sleep-wake cycles in the general population as well as in shift worker populations (Fischer et al. 2016). For that purpose, intrinsic biological night can be estimated indirectly in an individual by identifying their chronotype with a validated scale such as the reduced Horne-Östberg Morningness-Eveningness Questionnaire (rMEQ) (Adan and Almirall 1991). The rMEQ correlates with the phase position in various endogenous circadian rhythms (Baily et al. 2018; Duffy et al. 1999; Horne et al. 1980; Horne and Östberg 1977; Thun et al. 2012). The mistiming of sleep and waking behavior from the intrinsic circadian rhythm is then quantified by (1) the distance of occurrence of sleep from the biological night and (2) the day-to-day variability of sleep timing. The CPD is consistent with other measures of circadian misalignment, such as inter-daily stability and behavioral entrainment of rest-activity rhythms (Fischer et al. 2016).

The risk for adverse cardiovascular outcomes is demonstrably more prevalent in emergency medical rescue workers and police officers compared to that of the general population (Zimmerman 2012). These individuals work in chronic high stress occupations and routinely perform shift work. Based on the relationships outlined above, we hypothesized that HR would be higher and HRvar would be lower in preferred evening types compared to preferred morning types. If a difference in these cardiovascular health markers during sleep and/or wakefulness would be found, we asked whether it was predicted by chronotype itself or the magnitude of circadian misalignment as quantified with individual constituent CPD scores.

Methods

Study participants

The recruitment and the demographic characteristics of the study participants have been described in detail elsewhere (Clark, Stucky et al., submitted). In brief, a total of 89 individual emergency medical rescue workers (n = 61), police officers (n = 25) and emergency doctors (n = 3) of both sexes (48 females) were recruited from urban locations in the greater Zurich, Switzerland, area. They took part in a study examining sleep and resilience to psychological stress and trauma. Recruitment occurred by means of flyers, email and presentations of the study at shift change. All experimental procedures were approved by the ethics commission of the canton of Zurich (# 2016-01357). Written informed consent was obtained prior to participation in the study. Inclusion criteria were met by all participants, which stipulated an age between 18-65 years (mean age of study population: 33.9 $\pm$ 7.7 years), body mass index (BMI) $\leq$ 25 (or if exceeding a BMI of 26, no reported sleep problems; mean BMI: 23.9 $\pm$ 3.0 kg/m^2), employment in one of two emergency rescue stations and one police station volunteering for the study, ownership of a smart phone and German language fluency. Exclusion criteria were: presence of a neurological disorder diagnosis or head injury with potential to influence electroencephalographic outcomes, excessive alcohol consumption of (> 5 alcoholic beverages/week) or a urine drug screen (Drug-Screen Multi 12-AE, Nal von Minden GmbH, Regensburg, DE)

revealing substance use. Participants in this study worked rotating shifts, which varied by occupation, such that emergency medical rescue workers (and emergency doctors) worked cycles of two 12-hour day shifts, followed by a free day and then two 12-hour night shifts and then four free days. Police officers worked in 6-day cycles, in which they worked four days with variable activity and bedrest times, concluded by two free days. Officers worked 37.5 hours in the four work days. Individual shift work schedules were not recorded.

Experimental Protocol

The study design comprised one month of continuous monitoring of wrist-derived rest-activity behavior including sleep, totaling 2,974 individual sleep episodes at various clock times over the day and night self-selected and initiated by study participants. Questionnaires assessing lifestyle, sleep and psychological variables in validated German version were filled out by participants. Upon successful completion of the study, participants were paid CHF 50 and provided with an individualized sleep report based on their own data, which was explained to them by a study staff member at debriefing.

Morningness-Eveningness Questionnaire – A Reduced Scale

We prospectively characterized the chronotype of individuals (n = 85 due to technical error) using the rMEQ (Adan and Almirall 1991). This shorter version of the original Horne - Östberg Morningness-Eveningness Questionnaire (Adan and Almirall 1991) includes five items, which focus on the morningness dimension from the total 19 questions of the original scale. The rMEQ demonstrates very comparable performance to the original questionnaire in terms of statistical correlation of outcome (r = 0.92, $p < 0.01$), reliability (Loureiro and Garcia-Marques 2015) and convergent validity (Adan and Almirall 1991; Caci et al. 2009; Chelminski et al. 2000). It was validated against actimetry (Natale et al. 2006a; Thun et al. 2012) and skin temperature (Weidenauer et al. 2019). Scores of the rMEQ range from 4 to 25, with higher scores indicating greater morningness.

Based on their rMEQ scores, the sample of 85 individuals was comprised of 1 definitely morning type, 19 moderately morning types, 45 neither types, and 20 moderately evening types. After viewing the bimodal distribution of the rMEQ scores in our data set (see Fig. 2 in Clark, Stucky et. al, submitted), we divided the sample in a data-driven approach by median split into two groups. The group of preferential evening types had a rMEQ score $\leq$ 14 (n = 42) whereas the group of preferential morning types had a rMEQ score > 14 (n = 43). The two groups did not differ systematically with respect to their demographic characteristics with the exception of age, such that the preferential evening types were slightly younger than the preferential morning types (31.3 $\pm$ 4.9 *vs.* 36.7 $\pm$ 9.2 years; p <0.01).

Wrist Activity and Wrist HR Monitoring

The commercially available fitness tracker Fitbit Charge 2™ (Fitbit Inc., San Francisco, CA, USA) was used, to record wrist activity utilizing accelerometry and wrist HR with photoplethysmography (PPG). It was worn continuously by all participants on their non-dominant wrist for one month. This device uses these wrist activity and HR data to generate variables with a proprietary algorithm capturing sleep timing, duration and quality, as well as sleep macrostructure. The Charge 2™ produces two types of sleep macrostructure variables. The "stages" type is composed of "light," "deep," "rapid-eye-movement (REM) sleep" stages, as well as "waking" in 30-s epochs when certain criteria are fulfilled, i.e., PPG signal quality is sufficient, sleep episode is > 3 hours in duration and sufficient battery charge is present. If these criteria are, however, not met then the alternative sleep macrostructure variables are produced, namely the "classic" type, which are "restless," "sleep" and "waking," with a resolution of 60 seconds. The sampling frequency of Charge 2™ HR data varies, but mean sampling frequency was 7.37 values per minute in our data set (Stucky, Clark et al 2020, submitted). For this reason, it was not possible to compute conventional variables of heart rate variability (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996), which rely on the inter-beat intervals of normal-to-normal peaks of the QRS wave complex recorded typically by means of electrocardiogram (ECG). We have instead taken the variance of the distribution of HR data (HRvar) captured by the Fitbit PPG as a substitute.

Figure 4.1 Heart rate and heart rate variability during sleep

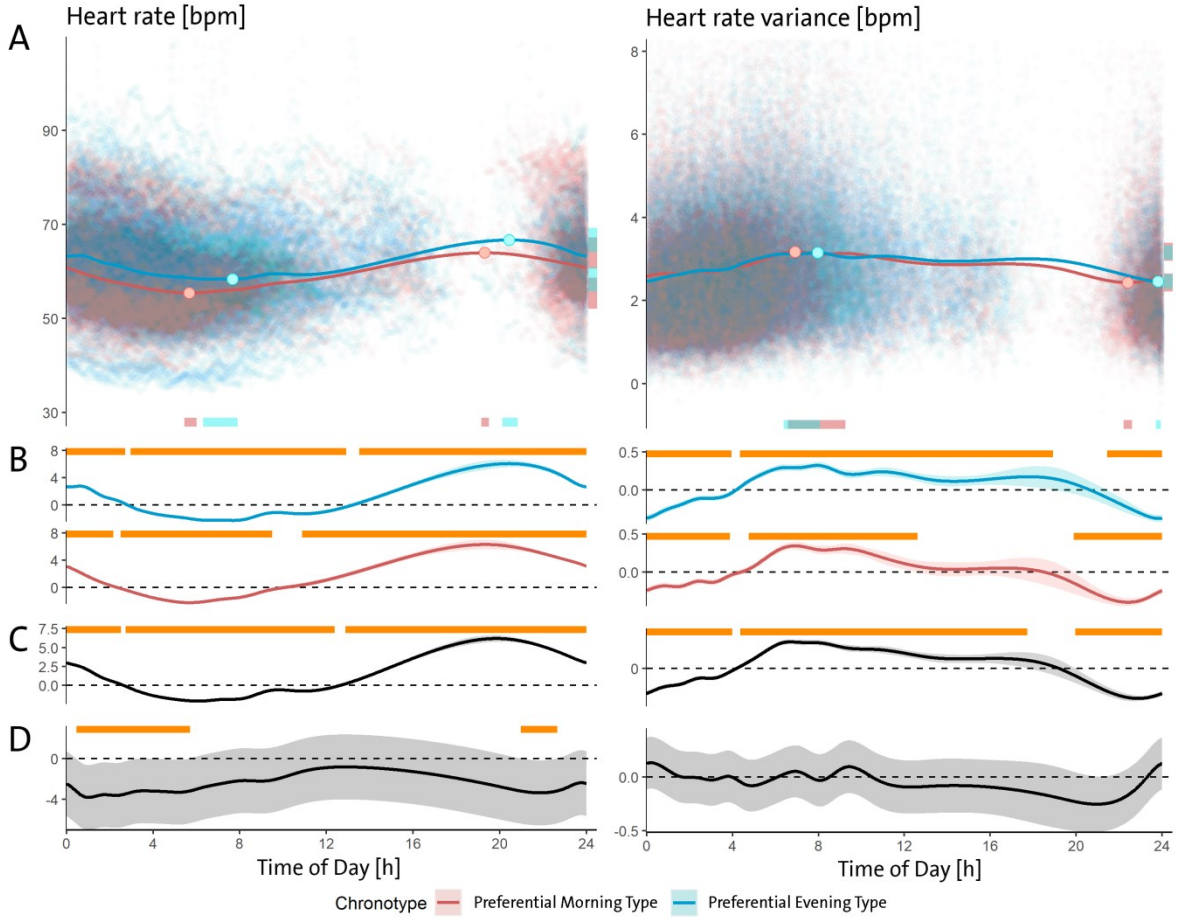

Figure 4.1 Heart rate and heart rate variability during sleep. Variations in the occurrence and internal organization of heart rate (HR; left) and heart rate variance (HRvar; right) during sleep across the day derived from Fitbit sleep data. Preferential Morning Type (n = 43) and Preferential Evening Type (n = 42) data are plotted in red and blue. All plots have time of sleep onset in hours as the horizontal axis. Panel A displays individual data points, their averages (curves), as well as peak and nadir (circles on curves). The vertical axes of HR and HRvar displays bpm. Confidence intervals are displayed (bar shapes color-coded to match the respective chronotype) and are displayed horizontally beneath and vertically to the right of panel A. Panels B, C and D display non-linear diurnal modulations over time of day and 95% confidence intervals (shaded area around curves); the vertical axes are in arbitrary units; orange bars of panels B and C indicate that values differ significantly from intercept (dashed line). Panel B displays data per chronotype, whereas panel C shows data for the entire sample. Panel D shows the difference between the chronotypes and orange bars indicate where their waveshapes differ significantly from one another.

Composite Phase Deviation (CPD)

The CPD can be computed from any variable collected as a time series and yields a vector length of 0 to 10, whereby increasing length indicates greater deviation. The CPD for sleep onset (ΔSO), sleep duration (ΔSD) and midpoint of sleep (ΔMid) was calculated in accordance to Fischer et al. (2020). We could not correct for social jetlag on weekends such as in Fischer (2020), as this sample consists of shift workers with variable, and to us unbeknownst, days off work. We further split off the irregularity of midsleep into its two components, an irregularity due to initiating sleep and an

irregularity due to staying asleep. The definition of CPD is thus composed of $\Delta M_t := \frac{1}{|t|}\sum_t var_t - var_t$ how far off a given day is from the average and $\Delta D_t := var_{t-1} - var_t$ the distance to the preceding day, here var_t either stands for S_{on}, S_d or $S_{mid} = S_{on} + \frac{1}{2}S_d$ of sleep episode t of a given subject, while $|t|$ denotes the number of sleep episodes of that subject. The formula reads as: $CPD_t{}^{var} := \sqrt{\Delta M_t^2 + \Delta D_t^2}$. Furthermore, the mean version of CPD over all sleep episodes of a subject (except for the first measured sleep episode of that subject, as no var_{t-1} can be calculated) is defined as $CPD^{var} := \frac{1}{|t|-1}\sum_t CPD_t{}^{var}$. This value is used in the models predicting HR and HRvar in NREM and REM sleep episodes.

Figure 4.2 Dynamics of heart rate

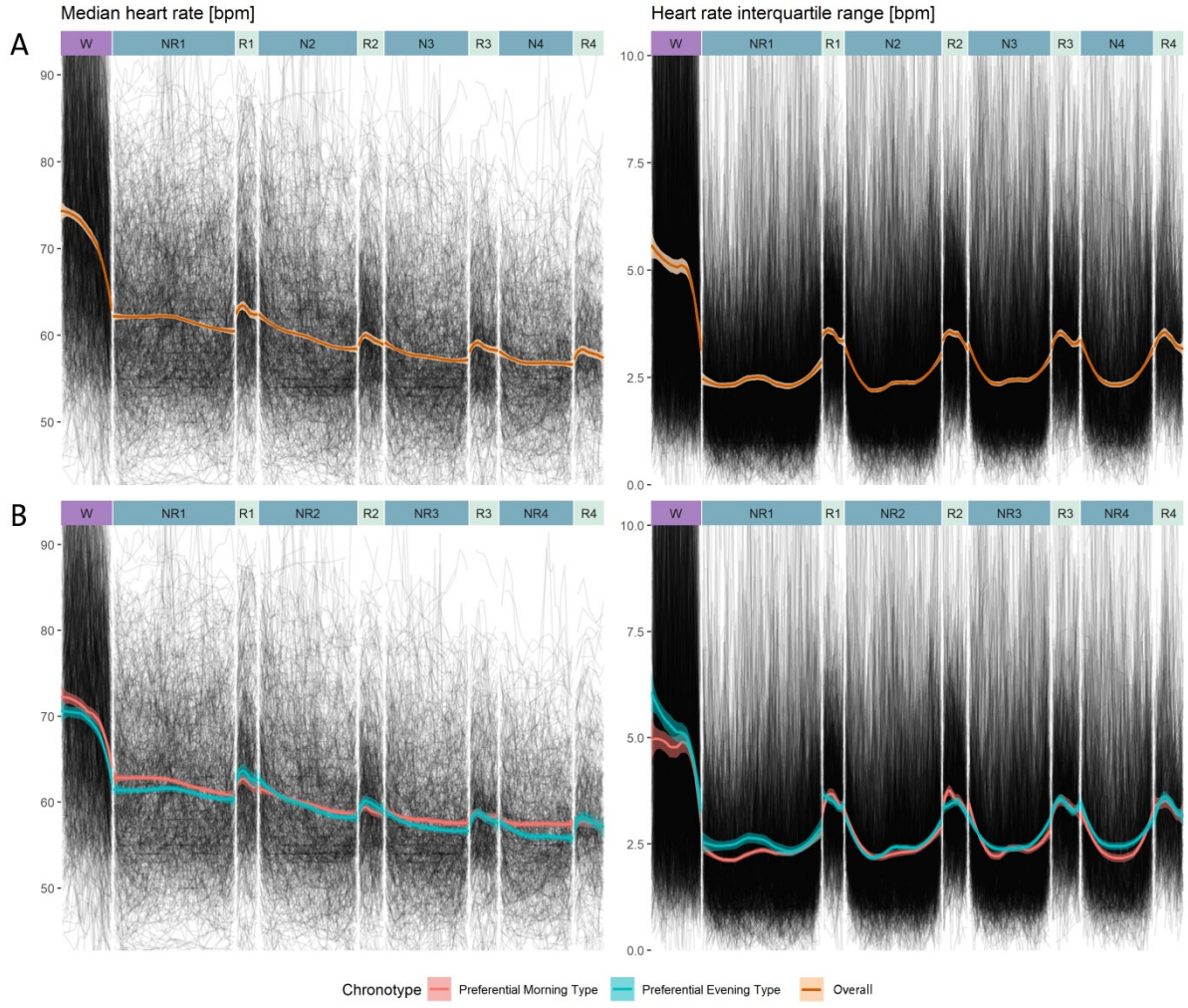

Figure 4.2 Dynamics of heart rate (HR) and heart rate variability (HRvar). The dynamic of HR and HRvar data from Fitbit Charge 2™ during sleep onset and across the first four NREM-REM sleep cycles during nocturnal sleep episodes initiated between 20:00 – 02:00 is shown (n = 89). We computed the relative lengths of each consecutive NREM and REM sleep episode from Fitbit as the average duration of the episode from NREM-REM sleep cycles 1, 2, 3 and 4. Forty-five minutes of wake before sleep onset are added to see the HR and HRvar changes around sleep onset. Each episode of the cycles is labeled with the sleep state: wake (W), NREM sleep episodes 1-4 (NR1-NR4), REM sleep episodes 1-4 (R1-R4). The estimated

curve is a GAM evaluated per episode, such that the curve displays non-continuous points at the ends and beginnings of each NREM and REM sleep episode. Making use of an estimation per episode instead of one single smooth estimation over the whole horizontal axis has the advantage to reflect the up- and/or downregulation of HR and HRvar occurring at transition from NREM to REM sleep and REM to NREM sleep more accurately. Left panel: Median HR (bpm) values are plotted on the vertical axis; Right panel: the vertical axis shows the interquartile range of HR (bpm). Raw data of individual sleep episodes is plotted in black.

Statistical Analysis

Comparisons of demographic data by chrontoype group were conducted in *R* (version 4.0.0) or in SAS (version 9.4, Cary, NC, USA) with Mann-Whitney *U* Test or Fisher's Exact Test where applicable. All further statistical analyses and plots were carried out in the statistical programming environment *R* (version 4.0.0). Statistical significance was set at an α of $p < 0.05$.

The analyses for the repeated measures and non-linear HR and HRvar 24-hour time courses were carried out with generalized additive mixed models (GAMMs) with Gaussian errors as implemented in the *mgcv* package (version 1.8-31). Linear correction terms for age and sex were included and knots fixed at 0 h and 24 h for continuity around midnight. Here HR and HRvar denote values from 3-minute moving median and moving interquartile windows with a shift ranging from one Fitbit HR value to the next. This ensures robust HR and HRvar values. Smoothing was applied with the *smooth.spline()* function with a smoothing parameter of 0.3 in *R* to make the discrete values from the moving median and moving interquartile functions follow a smooth curve. Conventionally computed HRV measures rely on knowledge of inter-beat intervals (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996), which Fitbit does not provide, and thus our robust variance measure can be thought of as a Fitbit-derived proxy of HRV. To be able to compute the plots on a PC with 16 GB of RAM, only every 30th heart rate and heart rate variance point was displayed. Simultaneous confidence intervals that correct for multiple testing in a continuous fashion were computed with posterior simulation on the GAMM with 100,000 random samples via modifications to functions in the *gratia* package in *R* (version 0.4.1). Occasional outliers of HR during sleep above 110 bpm and HRvar of more than 9 bpm were removed to not skew the results. The plots display the model estimate for a female with age 23 years. Seventeen degrees of freedom were used in the models to capture local increases in HR and HRvar while avoiding overfitting.

The NREM-REM sleep cycles from Fitbit sleep "stages" data were computed with the criteria provided in Feinberg and Floyd (1979). For the statistical analyses of HR and HRvar within consecutive NREM or REM sleep episodes, linear mixed effects regression (LMER) in the package *lme4* (version 1.1-21) was used. At first, all sleep episodes were included with random intercepts per sleep episode nested inside of the subject identifier, but the residuals did not fulfill the required assumptions, even after applying various transformations, such as different random effect structures and the use of generalized versions of linear mixed models. Hence, we decided to use average HR and

HRvar values per individual and per NREM and REM sleep episode, which reduces the complexity of the repeated measure structure considerably. These average models fulfill the assumptions on the residuals very well, and thus we only report them. P-values as computed by the *lmerTest* package (version 3.1-11) and the correlation matrix via the *corrplot* R package (version 0.84) are corrected per model for multiple testing with the Benjamini-Hochberg (BH) procedure controlling for the False Discovery Rate (Benjamini and Hochberg 1995).

Results

Cardiac-autonomic outcomes during sleep across 24 hours in the entire sample

When plotting the HR and HRvar data as function of time when all 2,974 individual sleep episodes were initiated, we observed diurnal oscillations in the waveshapes of these variables during sleep, as evident from the difference from intercept at many clock times and the occurrence of amplitude maxima and minima (**Figure 4.1**). Mean HR during sleep across 24 hours showed an approximate sinusoidal waveshape, such that the maximum of 66.16 bpm (95% confidence intervals: 63.73, 68.64 bpm) was observed in the evening at 19:50:53 (19:43:41, 20:02:24), whereas the minimum of 57.88 bpm (55.44, 60.34 bpm) was observed in the morning at 06:05:46 (05:42:43, 06:17:17) (**Figure 4.1C)**. Examination of HRvar (bpm) during sleep also revealed diurnality in the distribution of this variable, such that the maximum of 3.14 bpm (2.98, 3.30 bpm) occurred at 06:41:46 (06:28:48, 08:03:50), whereas the minimum of 2.50 bpm (2.31, 2.63 bpm) occurred at 22:53:46 (22:40:48, 23:11:02), approximately mirroring the HR maximum and minimum in the inverse at these time points. Male and female individuals differed trendwise ($p = 0.07$) with respect to 24 h sleeping HR (-2.66 bpm)) but not with respect to HRvar. A trend was detected regarding age, such that the older an individual's age, the higher their HR was observed to be on average in sleep across 24 hours ($p < 0.07$). This association was accompanied by the opposite pattern in HRvar, which decreased as age advanced ($p < 0.05$). No influence of age was observed in waking HR or HRvar.

Cardiac-autonomic outcomes during sleep across 24 hours by chronotype

The HR data of individuals characterized for morning or evening activity preference assumed an approximate sinusoidal waveshape (**Figure 4.1B)**. Average HR was greater in Preferential Evening Types from 00:27:22 to 05:42:43 as well as from 20:58:34 to 22:39:22 compared to Preferential Morning Types (2.94 bpm). The phase position of HR minimum of 55.40 bpm (52.06, 58.68 bpm) was advanced at 05:39:50 (05:26:53, 06:00:00) among Preferential Morning Types relative to the HR minimum of 58.32 bpm (55.74, 60.87 bpm) of Preferential Evening Types, whose HR minimum occurred at 07:40:48 (06:18:43, 07:53:46). The HR maximum of 63.93 bpm (60.58, 67.26 bpm) was advanced in Preferential Morning Types occurring at 19:19:12 (19:09:07, 19:30:43) compared to Preferential Evening Types, which was 66.66 bpm (64.12, 69.25 bpm) at 20:26:53 (20:08:10, 20:49:55). With respect to HRvar, a phase advance in HRvar of 2.43 bpm (2.21, 2.65 bpm) at 22:24:58

(22:13:26, 22:36:29) was observed in Preferential Morning Types compared to the HRvar minimum of 2.28 bpm (2.28, 2.63 bpm) at (23:49:55, 23:57:07) of Preferential Evening Types. On average, HR was higher in Preferential Evening Types across 24 h compared to Preferential Morning Types ($p < 0.05$).

Cardiac-autonomic dynamics during nocturnal NREM-REM sleep cycles

The upper panel of **Figure 4.2** illustrates the evolution of HR and HRvar dynamics during 45 min before sleep onset and across the first four NREM-REM sleep cycles of nocturnal sleep episodes initiated from 20:00 to 02:00.A global declining trend was observed in median HR across all cycles. Ultradian variation in HR is characterized by gradual decline across consecutive NREM sleep episodes, terminating in a slight increase that is following by an explosive surge in HR at REM sleep transition. During REM sleep episodes, HR peaks in the approximate first one third of the episode, followed by a gradual decline before flowing into NREM sleep. When examining these data by chronotype, HR begins higher in Preferential Morning Types than in Preferential Morning Types during wake before sleep onset and generally appears to remain higher during NREM sleep episodes, whereas this pattern switches during the first two REM sleep episodes. An opposite pattern is observed in HRvar, such that HRvar is higher during waking and NREM in Preferential Evening Types but this switches during the first two REM sleep episodes, such that HRvar becomes lower during the first two REM sleep episodes.

Cardiac-autonomic outcomes and circadian misalignment during nocturnal sleep

Cardiac-autonomic outcomes HR and HRvar during the first four NREM-REM sleep cycles were examined in relation to the degree of circadian misalignment quantified by CPD derived from sleep onset times (ΔSO) for nocturnal bedrest. As illustrated in **Figure 4.3**, the degree of ΔSO profoundly impacted cardiac-autonomic outcomes, such that as ΔSO increased, so did HR and HRvar.

Figure 4.3 Circadian phase deviation of sleep onset

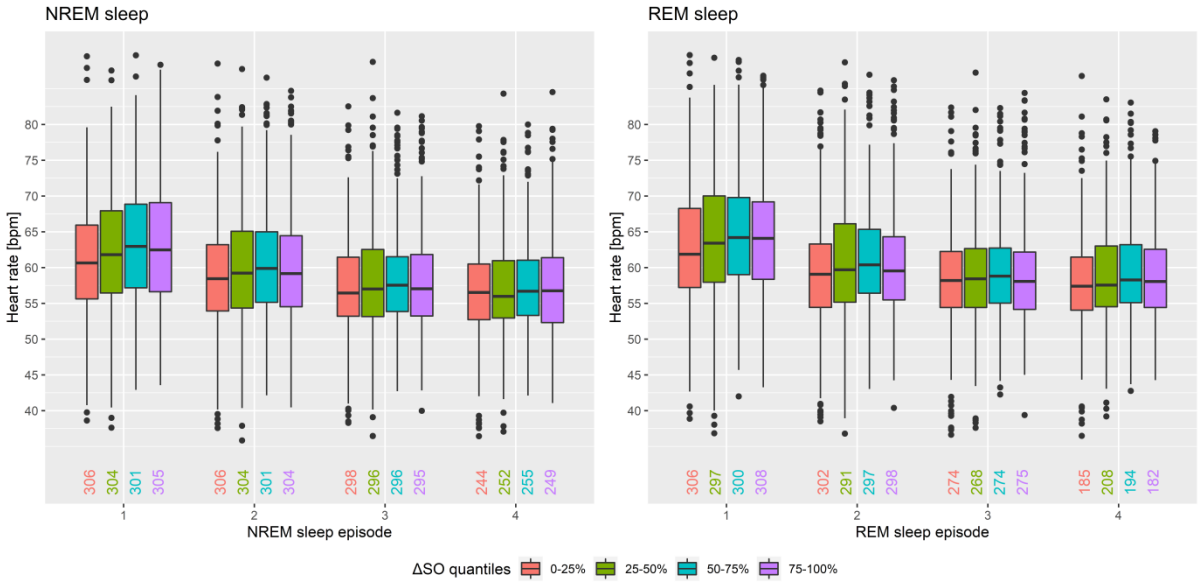

Figure 4.3 Circadian phase deviation of sleep onset (ΔSO) modulates heart rate (HR) in the first four nocturnal NREM (left panel) and REM sleep (right panel) episodes (n = 89). Sleep episodes were initiated from 20:00 to 02:00. The vertical axes display HR in bpm. The horizontal axes show ΔSO quantiles, which are color-coded. The number of nocturnal sleep episodes which contributed to each quantile is indicated vertically beneath the respective quantile in a color-congruent manner. Box and whisker plots display median, interquartile range and upper and lower bounds. Individual data points represent outliers.

Cardiac-autonomic outcomes and circadian misalignment during nocturnal sleep by chronotype

A correlation matrix shows that changes in HR were associated with ΔSO (**Figure 4.4**).

Figure 4.4 Correlation matrix of circadian phase deviation and chronotype

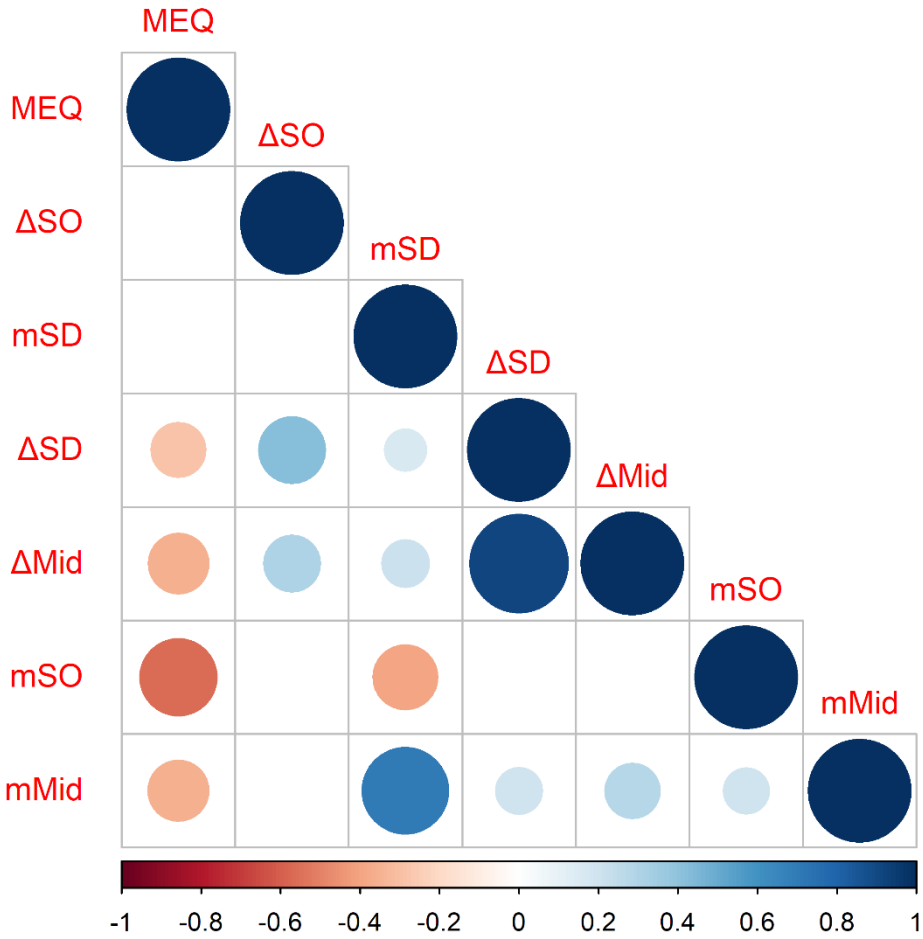

Figure 4.4 The CPD was quantified by selected variables of nocturnal sleep timing in individuals characterized for circadian type (n = 85). MEQ = Horne-Östberg Morningness-Eveningness Questionnaire; ΔSO = CPD of sleep onset; mSD = mean sleep duration; ΔMid = CPD of sleep episode midpoint; mSO = mean sleep onset time; mMid = mean sleep episode midpoint. Statistical significance is indicated by the presence of circles (i.e., their absence indicates no statistical significance) and their circumference (significance increases with circumference). Color indicates direction of correlation on a continuum from red to blue, such that red is negative, whereas blue is positive.

Discussion

The objective of this study was to characterize cardiac-autonomic activity during sleep in a sample of emergency medical rescue workers and law enforcement officers performing shift work under naturalistic conditions for one month. We examined HR and HRvar with the Fitbit Charge 2™ during sleep occurring at many different clock times over 24 hours. We could demonstrate that despite workers' efforts to make their sleep/wake cycles align with shift work schedules, intrinsic circadian

rhythms of cardiac-autonomic activity still entrained to the 24 h light/dark cycle persisted, indicating that physiological adaptation was unsuccessful and circadian misalignment was present, reflected in CPD values. This is not surprising, given that it takes approximately 1 day to phase shift 1 hour in jetlag scenarios (Rüger and Scheer 2009), and individuals in this sample are not allotted a sufficient number of days between shift rotations to achieve alignment between behavioral cycles and endogenous circadian rhythms. The amplitudes of the observed evoked circadian rhythms of HR and HRvar were blunted appreciably due to masking factors (e.g., light exposure, physical activity, knowledge of clock time, meal times, etc.), but the rhythms were nevertheless very much intact and largely congruent to those observed under constant routine or forced desynchrony conditions in laboratory settings (Baehr et al. 2000; Kräuchi and Wirz-Justice 1994b; Scheer et al. 2009). Individuals characterized for circadian typology in this sample provide further substantiating evidence that we were successful in capturing actual rhythms of inherent circadian cardiac-autonomic processes, as the familiar systematic variability in relative phase position between individuals with a morning and evening preference were readily apparent in both HR and HRvar rhythms. That individuals with an evening preference were observed to have a higher average sleeping HR across 24 h but no difference with respect to HRvar compared to individuals with a morning preference suggests a relative impairment in autonomic regulation in these individuals. It is reasonable to conclude that intrinsic circadian and homeostatic differences in chronotype actually underlie such a finding because these individuals did not differ with respect to sex, BMI or surveyed lifestyle factors, such as physical recreation habits or intake of psychoactive substances, known to impact autonomic function. Evening types were younger than morning types, and while this difference was statistically significant, it amounted to only five and half years on average. In general, the sleep of older adults (>65 years) is of poorer quality than younger adults and is characterized by longer sleep latencies, shorter sleep durations, diminished markers of homeostatic rebound and proportionately more 'light' sleep stages at the expense of 'deep' sleep stages (Crowley 2011). Autonomic function in older adults shows diminished markers of parasympathetic HRV and increases in markers of sympathetic HRV (Brandenberger et al. 2003). Differences with respect to cardiac-autonomic function have been found between evening types and morning types, such that morning types have been observed to have a higher HR and BP in the morning hours, whereas these respective processes are higher in evening types in the evening. Reactivity to a stress task was higher in both groups at chronotype-incongruent time of day (Nebel et al. 1996; Willis et al. 2005). Griefahn (2002) observed higher average HR in morning types under constant routine conditions, whereas Roeser et al. (2012) showed that morning types had a lower HR, diastolic blood pressure but higher vagal HRV compared to evening types. The extent to how the autonomic system behaves in individuals with different chronotypes under shift work conditions has received little scientific attention.

Although HR was higher in Preferential Evening Types compared to Preferential Morning Types, increased HR in Preferential Evening Types was negatively associated with mSO, mMid,

ΔMid and ΔSD but not associated at all with ΔSO and mSD (**Figure 4.3**), yet ΔSO modulated HR (**Figure 4.4**). One may conclude from these findings that it is irregularity of sleep onset and hence circadian misalignment *per se* rather than shorter sleep duration or chrontype which elevates HR. Moreover, ΔSO was positively correlated with ΔSD and ΔMid.

We investigated the ultradian dynamics of heart function throughout sleep onset and during the first four NREM-REM sleep cycles of nocturnal bedrest. The NREM-REM sleep cycle modulates HR and HRvar over the sleep episode. The observed increase in HR and particularly in HRvar during NREM sleep which precede transition to a REM sleep episode support the notion that cerebral events which lead to transition from NREM to REM sleep occur before electrophysiological manifestation of this sleep state. Our observations derived from wrist activity and PPT are in close accord with previous laboratory polysomnographic findings in humans (Bonnet and Arand 1997; Cajochen et al. 1994; Viola et al. 2002). Surges in cholinergic brain stem activity precedes REM sleep transition by 1 minute in cats (Steriade et al. 1990). Increases in HR and BP precede arousals by 3 – 6 seconds, and cardiac-autonomic activity precedes transition to slow wave sleep (SWS) (Trinder et al. 2012).
The both longitudinal and ecological design of this study favors the external validity of its findings. The rotating shift work schedules of our sample permitted us to collect cardiac-autonomic data in nearly 3,000 sleep episodes scattered across many times of the day and night and capture the intrinsic circadian rhythms of HR and HRvar during sleep in 89 individuals of varying ages and both sexes. This relatively large sample size boosts our confidence that what have observed is real. One could argue that the sample of first responders we investigated here is not representative of the general population or even of other shift workers, as first responders are exposed routinely to higher levels of danger and trauma, underlying the relatively high prevalence of trauma and stressor-related disorders in these occupations (Berger et al. 2012). This may well be the case; however, we did not detect above normal levels of perceived stress or posttraumatic stress in our sample. We conscientiously applied minimal inclusion or exclusion criteria to our sample, and it is reasonable to assume that this increased the heterogeneity of our sample and very likely diminished the signal to noise ratio. We, nevertheless, view this not as a weakness since the patterns of sleep and cardiac-autonomic rhythms we detected were very robust, confirming and extending findings arrived at by means of constant routine and forced desynchrony protocols under highly controlled laboratory conditions in healthy individuals. Of course, we were unable to collect data from all clock times, as relatively few individuals in our sample elected to sleep between the hours of 16:00 and 20:00, a timespan corresponding to the evening wake maintenance zone (Dijk and Czeisler 1994) or possibly latent social pressures. In addition, the presence of masking factors precluded measurement of an individual's endogenous circadian period. Fitbit makes HR data available to the public at a low level of granularity. For this reason, it is not possible for investigators to compute the conventional variables of heart rate variability, as their calculation relies on intervals between normal R peaks of the QRS complex, reducing the degree of comparability of our findings with those of other investigators who used ECG. The PPG of the Charge

2™ device collects pulse data on the order of individual beats, but these raw data are not relinquished by Fitbit. Fitbit employs an algorithm to estimate sleep macrostructure, and that algorithm is a trade secret, preventing insight into how variables are operationalized. This wearable device was, furthermore, developed for recreational use in consumers and not specifically for clinical or research purposes (de Zambotti et al. 2019).

Future research should continue to conduct naturalistic studies utilizing large sample sizes to bridge the gap between experimental controlled laboratory studies and epidemiological studies. Longitudinal study designs benefit knowledge about the dynamics of cardiac-autonomic processes and sleep across prolonged time periods. Work schedules of participants should be documented and verified by some objective means, e.g., wrist activity. Other populations should be investigated, such as those in disease-risk groups. There is pressing need for evidence based guidelines to inform effective countermeasures for individual shift workers.

In conclusion, we observed that first responders who engage in shift work exhibited behavioral and cardiac-autonomic patterns of profound circadian misalignment, which was not modulated appreciably by an individual's chronotype in our sample. On average, we could show that Preferential Evening Types had a higher HR but not HRvar during sleep compared to Preferential Morning Types, and that this was particularly the case for nocturnal sleep episodes. Circadian misalignment quantified by nocturnal ΔSO revealed that Preferential Evening Types suffer a relatively greater degree of circadian misalignment than Preferential Morning Types. Neither chronotype group was, however, able to successfully adapt their sleep/wake behavior to their shift work schedule to an extent that resulted in a phase shift of their intrinsic circadian rhythm away from entrainment to the 24 h solar day. The persistent approximate sinusoidal circadian oscillation of HR and HRvar was evident across all individuals, regardless of chronotype. Furthermore, the ΔSO values for all individuals demonstrated circadian misalignment. This carries potentially serious health implications for those individuals performing shift work.

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The authors declare no conflict of interests.

5. Discussion

5.1 Summary

The aims of this thesis were to longitudinally characterize the rest-activity behavior of a sample of first responder emergency medical rescue workers and law enforcement officers performing shift work under naturalistic conditions with a commercially available wearable device (Fitbit Charge2™) and ambulatory polysomnography (PSG). I sought to ascertain to what extent the demands of their profession including shift work interfere with their sleep quantity and quality, as well as with healthy cardiac-autonomic function. Phrased differently, how tolerant were these individuals to the challenge of shift work? Sleep variables were operationalized with the conventional variables of sleep duration, wake after sleep onset (WASO), rapid eye movement (REM) sleep latency, and REM sleep percentage. Variance in the preferential management of sleep episodes and their duration across a 24-hour period for everyone over the one-month study period was also investigated. A variety of demographic, clinical, health and lifestyle variables were surveyed in this sample and a selection of these variables was used as covariates in analyses related to sleep to determine to what extent observed inter-individual variability may be due to differences in, for example, chronotype, sex, age and varying rates of caffeine and alcohol consumption as well as physical fitness.

One of the aims was to capture the profile of selected cardiac-autonomic endpoints (mean and variance of heart rate [HR]) during sleep and waking. An emphasis was placed on the development of these variables within individual sleep stages (non-rapid eye movement [NREM] "light" sleep, NREM "deep" sleep and REM sleep) as constituents of the first four NREM-REM sleep cycles of the night. Considerable ultradian variability in both sleep structure and autonomic regulation is a salient feature of human sleep. Under normal conditions, autonomic regulation of the cardiovascular system varies within a given sleep state as well as in the transition from one state to another in a predictable fashion, whereby electrocardiogram (ECG) changes precede PSG indications of sleep state change by several minutes (i.e., rapid HR acceleration preceding REM sleep and gradual HR deceleration preceding NREM sleep). A global trend of gradually decreasing heart rate is observed for the entire sleep episode, and the evoked circadian rhythm has been well established in both selected sleep (e.g., REM sleep) and cardiovascular (e.g., HR) endpoints. I sought to investigate the extent to which this pattern persists under naturalistic conditions during shift work and at varying times of day in my sample and to establish a link to the highly prevalent phenomenon of circadian misalignment, which frequently accompanies shift work.

In the interest of elucidating further inter-individual differences in preferential management of rest-activity behavior, individuals were stratified in the sample by score on the highly validated and widely used Horne-Östberg Morningness-Eveneningness Questionnaire – A Reduced Scale (rMEQ), which assesses a trait-like behavior influencing the preferential timing of a variety of behavioral

cycles, such as sleep/wake and fasting/feeding, and is putatively driven, at least in part, by variance in genetic substrates, which underlie circadian and homeostatic characteristics, as well as by age and other environmental or psychological factors. In a data-driven approach, I created two groups of individuals in my sample, corresponding to the bi-modal distribution of rMEQ scores in my sample and compared these groups with respect to the distribution of variables of sleep quality and cardiac-autonomic function. I could show that Preferential Evening Types compared to Preferential Morning Types seem to cope differently with the demands of shift work, such that sleep of greater duration, which was more distributed across a given 24-hour period. The mean HR was higher in this group compared to the Preferential Morning Types. These findings are explored in more detail in chapters 3 and 4, manuscripts 2 and 3, respectively.

With the goal of demonstrating the integrity and validity of my Fitbit-derived findings, I conducted a validation study comparing Fitbit-derived variables of sleep quality and structure to counterparts derived from the gold standard of PSG, explored in Chapter 2, manuscript 1. This validation study demonstrates that Fitbit captures these variables with an accuracy and reliability that is at least sufficient to detect significant and robust differences in rest-activity behavior and cardiovascular regulation.

First responders

An above-average degree of resilience to post-traumatic stress is believed to characterize law enforcement or emergency medical rescue workers (Berger et al., 2012). There is a disproportionately low prevalence of post-traumatic stress-related mental illness in these first responder populations (4.7% and 14.60% respectively) despite rates of exposure to potentially traumatic events much higher than that of the general population (Berger et al., 2012). Indeed, such populations are exposed routinely to such events that would be sufficient to induce a trauma and stressor-related disorder in a member of the general population. The pooled worldwide prevalence of PTSD is 10% in first responders, compared to the 1.3 – 3.5 % observed in the general population (Berger et al., 2012). Chronic sleep disturbance is a cardinal feature of PTSD and has been suggested to play a major role in the pathogenesis and maintenance of the disorder, as reflected by the majority (70%) of individuals with a PTSD diagnosis who report clinically relevant sleep problems (Ohayon & Shapiro, 2000). Alterations in the sleep electroencephalogram, such as decreased deep sleep, increased arousals and wake after sleep onset have been identified compared to that of individuals without a PTSD diagnosis (Kobayashi, Boarts, & Delahanty, 2007). I chose to study first responders, as these comprise a vulnerable population exposed to stress and potentially traumatic events on a regular basis to ascertain the extent to which I could capture stress outcomes, cardiac-autonomic endpoints and sleep disturbance in this sample. The fact that this population performs shift work offered me the opportunity to investigate a potential role of shift work on stress, sleep and cardiac-autonomic endpoints. The primary aim in sampling this population was to capture sleep in the immediate

aftermath of a potentially traumatic event. I could then investigate the specific composition of a night of sleep post-trauma and make inferences on whether sleep after trauma exposure is a benefit or hindrance to the individual in coping with the trauma.

Shift work

Emergency medical rescue workers and police officers constitute an essential work force. Since disaster could strike at any moment, it is necessary for individuals in these frontline services to maintain around-the-clock vigilance, necessitating work outside the conventional working hours of 09:00 and 17:00 h. This requires that individuals maintain wakefulness during the biological night and sleep during the biological day. This is problematic, however, because the intrinsic circadian rhythms of various physiological processes are only poorly suited to support behaviors at odds with the appropriate circadian window of opportunity (Sletten et al. 2020). The outcome of behavioral cycles, such as sleep/wake or fasting/feeding, occurring at inappropriate circadian phases is referred to as circadian misalignment (Rüger and Scheer 2009).

Rest-activity behavior and sleep

I could show in study 2, chapter 3, that the frequency of sleep episodes, their composition and integrity were not randomly distributed across 24 h, with a pattern conforming to an approximate sinusoidal waveshape. Individuals appear to have initiated sleep episodes most frequently on the descending slope of their body temperature, indirectly assessed with patterns of latencies to REM sleep episodes and proportion of REM sleep episodes. This is in accord with findings from controlled laboratory studies (Czeisler et al. 1980b). The observation, however, that diurnal rhythms of sleep propensity and REM sleep composition were still entrained to the 24 h light/dark cycle across all subjects despite them performing shift work indicates that the sleep/wake cycles of individuals in this sample were misaligned from these entrained rhythms.

In study 2, chapter 3, it was demonstrated that Preferential Morning Types reached their sleep duration nadir sooner than Preferential Evening Types. No difference was observed in the phase positions of the zenith of sleep duration and WASO. Preferential Evening Types slept considerably longer than Preferential Morning Types in sleep episodes initiated at nighttime (+ 1.13 h), morning (+0.94 h), but not evening (- 1.0 h) hours, appearing to sleep whenever their environment and diurnal processes allowed. Bedrest was more consolidated among Preferential Morning Types in contrast and tended to occur more at nighttime and less during the daytime. I tentatively concluded from this observation that Preferential Evening Types in my sample may be differently equipped to tolerate the burden of shift work, possibly in a more adaptive manner, which might suggest greater flexibility in sleep-wake regulatory processes in these individuals than in Preferential Morning Types. This observation in conjunction with findings on morning types in the literature with respect to homeostatic sleep-wake regulation could lead one to speculate that evening types bear a higher homeostatic burden of sleep propensity compared to morning types, in some of whom faster accumulation as well as

dissipation of electroencephalographic markers of homeostatic sleep propensity has been observed (Mongrain et al. 2006). An interpretation of my data in keeping with these findings might be that morning types simply obtain the sleep they need at conventional nighttime hours of bedrest. Such a hastened ebb and flow of homeostatic sleep propensity in some morning types would fit a pattern of diminished sleep duration during the daytime and longer latencies to REM sleep episodes.

Cardiac-autonomic regulation and sleep

The cardiovascular system of Homo sapiens as in all mammals is tightly organized with respect to time (Chen and Yang 2015). The risk for morbidity and mortality due to adverse cardiovascular events is not distributed equally across 24 h, with greatest incidence between ~06:00 – 12:00 (Chellappa et al. 2019; Rüger and Scheer 2009). Circadian clocks are present in endothelial cells, cardiomyocytes and smooth muscle cells of the heart and influence diurnal cardiovascular function (Young 2006). The peaks of platelet surface activated glycoprotein as well as platelet count, adenosine triphosphate (ATP) release, aggregability and plasma epinephrine concentration show circadian rhythmicity (Scheer et al. 2011). Both HR (Kerkhof et al. 1998; Kräuchi and Wirz-Justice 1994a; Van Dongen et al. 2001) and heart rate variability (HRV) (Aoyagi et al. 2003) exhibit intrinsic circadian as well as homeostatic (Viola et al. 2002) variation under constant routine conditions. The absence of an endogenous diurnal rhythm in blood pressure (BP) under constant routine conditions (Kerkhof et al. 1998; Van Dongen et al. 2001) (cf. Millar-Craig et al. 1978; Scheer et al. 2009) however, may suggest that not all cardiac-autonomic system endpoints are governed exclusively by a circadian pacemaker and may instead be at least partially sleep-dependent processes (Viola et al. 2002).

In studies 2 and 3, chapters 3 and 4, respectively, I observed the persistence of an entrained diurnal rhythm despite sleep/wake cycles tailored to shift work schedules. In study 3, chapter 4, this fact is evinced by the endurance of diurnal rhythms of cardiac-autonomic activity of HR and HRvar entrained to the environmental *Zeitgebers* corresponding to the 24 h light/dark cycle. These cardiac-autonomic rhythms approximately mirrored rhythms of sleep duration and REM sleep variables and were the approximate inverse of the rhythm of WASO. This coherence of diurnal rhythmicity between REM sleep and sleep propensity and cardiac-autonomic activity is to be expected and lends confidence in my conclusion that I have captured actual physiological processes in my sample. The amplitudes of the evoked diurnal rhythms of HR and HRvar were blunted appreciably due to masking factors (e.g., light exposure, physical activity, knowledge of clock time, meal times, etc.), but the rhythms were nevertheless visibly intact and conformed to those observed under constant routine or forced desynchrony paradigms (Baehr et al. 2000; Kräuchi and Wirz-Justice 1994b; Scheer et al. 2009). The misalignment of these processes with sleep/wake cycles is further reflected in the high composite phase deviation (CPD) values. High CPD values indicate the presence of circadian misalignment in a given time series variable.

Chronotype and cardiac-autonomic endpoints

In study 3, chapter 4, I observed a higher HR during nocturnal sleep episodes, but not during daytime sleep episodes, in Preferential Evening Types compared to Preferential Morning Types. Expected phase advances in Preferential Morning Types were observed for both HR minimum and maximum and HRvar minimum compared to Preferential Evening Types. With respect to CPD, variability in time of sleep onset (ΔSO) was associated with elevated cardiac autonomic outcomes during the first NREM-REM sleep cycle of nocturnal sleep episodes in Preferential Evening Types. These findings fit in with what is known about evening types with respect cardiovascular health (Knutson and von Schantz 2018). My findings support a role of chronotype in individual differences in tolerance to shift work, but neither chronotype was successful in entraining to their shift work schedule as revealed by the degree of misalignment between diurnal rhythms of HR, HRvar and sleep-wake parameters. Failure or inability to entrain biological rhythms to behavioral cycles determined by the environment is associated with adverse cardiometabolic outcomes (Sletten et al. 2020). Evening types are more likely to suffer such negative health outcomes than morning types (Merikanto et al. 2013, Knutson and von Schantz 2018). It is believed that a greater degree of misalignment between endogenous circadian rhythms and behavioral cycles reflecting imposed external work schedules and social opportunities is evident in evening type individuals (Knutson and von Schantz 2018).

Validation of Fitbit Charge 2™ against polysomnography

In study 4, chapter 2, I validated a commercially available wearable sleep tracker by the manufacturer Fitbit called the Charge 2™ against ambulatory PSG. I could demonstrate that there was good agreement between the output of this device and that of PSG, bearing in mind certain limitations which shall be elucidated. I could show that indeed Fitbit sleep onset corresponded to PSG N1 sleep onset more closely, as reflected by a near absence of bias (~3 minutes) in sleep onset, whereas appreciable bias was observed in comparison to N2 sleep onset (~10 minutes). With respect to all stages and total sleep time (TST) did not reveal appreciable biases, although this varied with respect to which sleep onset criteria was adopted in analyses. Latency to REM sleep and proportion of WASO each revealed a bias of ~30 minutes. The large limits of agreement (LoA) suggest, however, that measurement of individual sleep episodes by Fitbit can deviate strongly. During sleep, Fitbit tends to underestimate HR by ~1 bpm with LoA of ~ -12 bpm and 14 bpm. Bias was greater for epochs of wake (~2 bpm) than for sleep (~<1 bpm), attributable most likely to the occurrence of artifacts during waking (which may have been present in the Fitbit HR data set). The variance of HR (HRvar) was underestimated with a bias of ~22 bpm compared to PSG HRvar, attributable to the lower data resolution made available by Fitbit (~7 measurements per minute) in HR, whereas in PSG ECG actual

inter-beat intervals are collected, a sensitivity of measurement that allows for capture of true variation in cardiac-autonomic function reflected by greater HRvar. The findings presented in this report need to be replicated in other populations, particularly those with sleep disorders or populations characterized by elevated risk for adverse cardiometabolic health consequences.

5.2 Clinical implications

It is estimated that approximately one third of individuals in the United States (ca. 110 million people) engage in shift work outside conventional daytime working hours (Alterman et al. 2013). The public health burden of shift work is substantial, with a yearly estimate of $71-93 billion in the United States, due solely to accidents behind the wheel and at the workplace traceable to excessive sleepiness (Culpepper 2010), to which shift work contributes significantly (Rajaratnam et al. 2013). This is, however, probably an underestimate of the true burden, since shift work and the often attendant circadian misalignment have far-reaching adverse health consequences (Sletten et al. 2020), whose costs must ultimately also be considered in the interest of any comprehensive estimate. Limited evidence (Gu et al. 2015) supports an increased total and cause-specific mortality in some shift work populations (cf. Hannerz et al. 2019).

Individuals in the current sample revealed sleep/wake cycles that were on average chronically at odds with their diurnal rhythms of sleep propensity, sleep duration, REM sleep and cardiac-autonomic function, which remained entrained to the 24 h light-dark cycle, indicating misalignment. I, furthermore, quantified this misalignment with CPD, which verified that these individuals had highly variable sleep/wake cycles. Individual differences in preferential management of rest-activity behavior revealed individual differences in chronotype, such that those who prefer evening activity distributed their sleep episodes more across the 24 h day compared to the pattern of sleep episodes in those individuals with a morning activity preference. Cardiac-autonomic markers differed between chronotypes, with evening types showing higher HR compared to morning types. This variability in preferential rest-activity management did not appear to impact the degree of tolerance of one chronotype over the other with respect to shift work. In other words, the environment was the critical factor in modulating diurnal rhythms, as evinced by enduring entrainment of all processes surveyed in this report.

It is a perennial question as to how an individual might best manage their behavior to boost tolerance to shift work (Östberg 1973). Chronobiology has revealed that the most powerful *Zeitgeber* entraining endogenous body rhythms to the exogenous environment is light. Energy in the form of photons enters the eye and is transduced by dedicated retinal ganglion cells into a biochemical signal that enters the brain via the retino-hypothalamic tract. At the point of decussation of the left and right tracts, known as the optic chiasm, this signal reaches a cluster of thousands of clock cells located in the hypothalamus, collectively called the suprachiasmatic nucleus (SCN). The SCN is the body's

master oscillator, setting and resetting the myriad clock genes expressed in cells in all tissues throughout the body. The result of a light impulse, depending on the circadian phase position of its presentation, is to entrain the processes to the external environment which has a periodicity of 24 h due to the light/dark cycle of the solar day. Since the human circadian rhythm is not precisely 24 h in its period and is typically slightly longer, this light impulse is needed to synchronize the various rhythmic processes of the body (Duffy and Czeisler 2009). In the context of modern civilization, which has changed radically over the past 100 years to see the advent and near omnipresence of artificial light, the natural light/dark cycle as being the primary determinant of behavior has waned considerably (Wickwire et al. 2017). Shift work is, for instance, facilitated completely by artificial light. As demonstrated in this report, diurnal rhythms entrained to the solar day persisted under shift work conditions. Current recommendations to boost an individual's tolerance to shift work and prevent shift work disorder (SWD) include napping and taking psychoactive substances promoting alertness (e.g., caffeine) before shift start, exposure to bright or blue-enriched light in the first half of shift, avoiding psychoactive substances in the second half of shift, avoiding bright light (e.g., wearing short wavelength light [blue] filter goggles) after shift end, creating a dedicated home sleep environment, consider melatonin, on free days maintain "anchor sleep" (partially delayed sleep overlapping with that of work day sleep) and seek social support (Wickwire et al. 2017).

Circadian misalignment of cardiac-autonomic rhythms of HR and HRvar could magnify vulnerability to cardiovascular disorders. One study demonstrated circadian misalignment by rapid 12 hour inversion of sleep/wake and fasting/feeding cycles impacted cardiovascular disease factors and elevated them to clinically relevant levels after only three days and is illustrated in **Figure 5.1** (Morris et al., 2016). With respect to HR, misalignment conditions raised 24-hour HR 1.6 bpm compared to aligned conditions.

Figure 5.1 Effects of experimentally induced circadian misalignment on heart rate

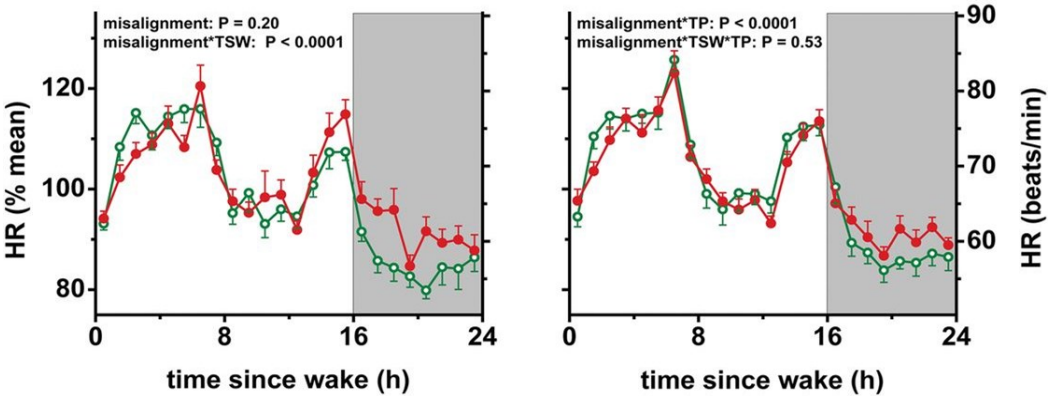

Figure 5.1 Effects of experimentally induced circadian misalignment on heart rate (HR) from Morris et al. (2016). Horizontal axis is time in hours (h) since wake. Gray area indicates sleep opportunity; white area indicates wake. Red curves represent circadian misaligned condition, green curves circadian aligned condition.

Test period (TP) indicates one of four periods of cardiovascular data sampling, each of which was preceded by isocaloric meal intake. Time since wake (TSW). Data are displayed as mean ± SEM.

During wake, HR was reduced by 0.9 bpm, and during sleep HR was increased by 3.6 bpm during misalignment conditions. The sleeping HR varied as a function of time in misalignment conditions, such that on day 1, the HR during sleep was increased +5.3 bpm, whereas on day 3 the increased was +2.0 bpm. These changes in HR were accompanied by changes in autonomic activity, such that HRV markers of vagal modulation were attenuated. The proportion of root mean square of successive differences (RMSSD) of normal R peaks intervals of the ECG was reduced by ~10% as was the proportion of the consecutive heart beat intervals differing by >20% (pNN20). This was most pronounced on the first day, such that the decrease in RMSSD was 15%. These changes in HR and HRV were accompanied by changes in BP. Circadian misalignment raised 24-hour systolic BP and diastolic BP by 3.0 mmHg and 1.5 mmHg, respectively. The magnitude of change in BP was comparable to that of dietary and pharmacological approaches to reduce hypertension (Mancia and Parati 2004; Moore et al. 1999). Although in the present study I did not collect BP data, the magnitude of change of the HR maxima and minima between chronotypes was ~3 bpm, respectively, with evening types having the higher HR (~67 bpm) during wake. The HRvar follows a similar pattern as HR, such that HRvar is diminished in evening types compared to morning types, although this was not statistically significant. A blunted or absent dip in HR and HRvar was not observed in my data. The HR and HRvar during sleep were within the range of what is reported for untreated hypertensive patients who were on average 20 years older than the average of my sample (Palatini et al., 2013). Hypertension is highly prevalent among shift worker populations and is associated with adverse cardiovascular events and cardiovascular disease. Studies show that the nocturnal sleeping HR is more prognostic of adverse cardiovascular consequences compared to daytime waking HR under entrained conditions. Given this information, the individuals in my sample may be at an elevated risk for clinically relevant health outcomes.

There is currently a gap in the knowledge of how best to translate and apply principles of chronobiology to shift workers to benefit their health and well-being (Wickwire et al. 2017). To bridge this gap, research on shift work populations is warranted. The efficacy and applicability of current recommendations to enhance tolerance for shift workers should be tested under naturalistic conditions in large and diverse samples. Wearable sleep trackers could benefit tolerance to shift work if accompanied by professional clinical guidance. If successful, this would improve the lives of shift workers and reduce the public health burden posed by this occupational arrangement.

5.3 Implications for future research

In this report, I investigated a sample of first responder shift workers characterized for their chronotype. First responders are not typical shift workers, however, and are characterized by routine

exposure to danger and potentially traumatic events, and it is for this reason that the prevalence of PTSD is greater in this population compared to non-first responder populations (Berger et al. 2012). My sample, interestingly, did not indicate higher levels of posttraumatic stress, perceived stress or depression compared to the general population when assessed by questionnaire. The sample was, however, in the 80th percentile for trait anxiety compared to the healthy adult population when assessed by the State Trait Anxiety Inventory (STAI) (Spielberger et al. 1983). One could speculate about why no elevated stress-related questionnaire outcomes were observed and surmise that since these individuals receive routine stress training to help them cope with life stress that this may have been sufficient to prevent excessive stress. More varied and in particular objective markers of stress, such as cortisol, should be collected in future studies in this or similar populations. I did not assess SWD directly in this sample, and it would have benefited my characterization of these individuals had I done so. Thus, questions probing somatic well-being, mood, food composition, hunger, appetite, meal timing, fatigue, daytime sleepiness and insomnia should be posed with some frequency to identify whether these variables reveal a pattern similar to those revealed in laboratory studies (Bonnell et al. 2017; Cain et al. 2015; Mason et al. 2020; Qian et al. 2019; Rüger and Scheer 2009). Measurement of neurohormones underlying hunger and satiety rhythms (i.e., ghrelin, leptin) might be sampled, in addition to markers of glucose tolerance and insulin resistance, as these have all been associated with detrimental outcomes related to circadian misalignment and shift work (Mason et al. 2020; Morris et al. 2015; Qian et al. 2019; Rüger and Scheer 2009; Scheer et al. 2009; Scheer et al. 2013). Study of the intrinsic circadian rhythm should be accompanied by measurement of body temperature and melatonin if possible. Naturalistic studies of free-running circadian rhythms in the blind with and without perception of light have utilized sampling of cortisol or urinary melatonin (6-suphytoxymelatonin) concentrations, the major metabolite of melatonin, to estimate dim light melatonin onset (DLMO), which is the gold standard for assessing the intrinsic circadian rhythm in humans (Lockley et al. 2007).

Future research into shift work and circadian misalignment should carefully document the shift schedules to differentiate between free and work days, as this has been shown to impact rest-activity behavior (Wittmann et al. 2006). Estimates of regularity in sleep episodes should be included, with measures such as CPD, as this is an effective and relatively sensitive means of capturing actual daily variability underlying circadian misalignment (Fischer et al. 2020; Fischer et al. 2016). Use of multi sensor wearable trackers can aid a study in more precisely measuring both movement and pulse. If possible, light exposure data should also be collected to aid in estimating the impact of this *Zeitgeber* in entrainment. Such trackers should be subject to critical review and validation, however, and guidelines for use in research and clinical undertakings is lacking as is United States Food and Drug Administration (FDA) regulation. The Oura Ring and Apple Watch are two promising devices which measure HR and wrist activity. Epoch-by-epoch comparison with PSG sleep/wake states showed d' between 1.78 and 1.87 and a sensitivity between 0.91 and 0.98 with specificity between

0.37 and 0.65 (Roberts et al., 2020). Review of the literature by Scott, Lack and Lovato (2020) suggests that commercial trackers overestimate sleep onset, but to a negligible extent.

I could show that chronotype modulated behavior and diurnal factors in a naturalistic shift work environment. Future studies should continue to investigate chronotype and identify to what extent age and sex affect this diurnal activity preference.

5.4 Conclusion

Shift work is here to stay. Despite a growing understanding of shift work and its involvement in circadian misalignment, there have to date not been effective countermeasures developed to prevent the risk for adverse health outcomes and disease associated with this condition (Silva et al. 2020; Wickwire et al. 2017). This calls for a greater understanding of the mechanisms which underlie circadian misalignment and individual differences in vulnerability to it. Next steps may involve further laboratory and naturalistic studies developed to test hypotheses derived from observations made in large epidemiological studies. This would help to bridge the divide presently between disease etiology and epidemiology in shift work populations and help develop therapies to improve the lives of shift workers.

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Ian Clark

PROFILE

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Date of birth / birthplace: 15.12.1981 / Exeter, USA
Civil status: married, three children (2016, 2017, 2020)

Citizenships: CH, USA

PROFILE

03.2016 – present Institute of Pharmacology and Toxicology of the University of Zurich, Zurich, Switzerland, Psychology, Ph.D. studies
Doctoral thesis: *Naturalistic studies on the effects of shift work-related circadian disruption on diurnal rest-activity behavior and cardio-autonomic patterns in morning and evening type police and rescue workers*

- Supervision of data collection in a clinical field study of 89 emergency workers to ascertain the role of chronotype on rest-activity behavior, sleep and cardiovascular health outcomes
- Drafting of clinical study documents for submission to ethics committees
- Creation of standard operating procedures on clinical study procedures involving blood drawing, DNA extraction, electrophoresis, PCR, genotyping, electroencephalography and computer-assisted clinical data collection
- Management and analysis of large datasets with SAS

09.2013 – 03.2016 University of Zurich, Zurich, Switzerland, Psychology, M.Sc., 5.5 / 6.0
Master's thesis: *Dopamine and sleep-wake regulation: effects of tolcapone and* DAT1 *genotype on sleepiness and rest activity patterns*

- Polysomnography
- Collection of human cognitive and electrophysiological data
- Drafting of grant application documents for financial support of analyses to quantify dopamine metabolites in human saliva samples
- Data analysis with SAS

09.2009 – 05.2013 Northeastern University, Boston, USA, Psychology, B.Sc., 3.72 / 4.0
magna cum laude

WORK EXPERIENCE

05.2020 – present Freelance clinical researcher for sleep studies

- Scoring of human polysomnography recordings for ETH Zurich, Mobile Health Systems Lab, Institute of Robotics and Intelligent Systems
  Department of Health Sciences and Technology, Zurich, Switzerland

09.2019 – present Scientific assistant, clinical research in PTSD University of Zurich, Clinic for Psychology, Psychotherapy and Psychosomatics,
Psychiatric University Clinic, Zurich, Switzerland

Project: Pharmacological prevention of post-traumatic intrusions in healthy volunteers – towards a post-exposition prophylaxis for PTSD

- Planning and design of a clinical sleep research project on secondary-prevention of PTSD through novel pharmacological means
- Writing of clinical documents for submission to ethics committees
- Development of study-specific documents, such as clinical questionnaires, statistical randomization protocols, illustrations of clinical procedures and clinical research timelines
- Drafting of grant applications

10.2018 – 03.2019 Clinical research associate, human sleep experiments
Clinic Barmelweid, Barmelweid, Switzerland

Project: Measurement of oxygen saturation of the brain and muscle by means of near-infrared spectroscopy (NIRS) during sleep

- Drafting of standard operating procedures for human sleep experiments, such as NIRS application and measurement, polysomnography, psychomotor vigilance tasks, CPAP, and clinical questionnaires
- Independent execution of polysomnographic and NIRS experiments in sleep apnea patients

10.2013 – 03.2016 Clinical research associate, human sleep experiments
Institute of Pharmacology and Toxicology of the University of Zurich, Zurich, Switzerland

Project: Roll of Catechol-*O*-methyltransferase (COMT) in the physiological regulation of vigilance

- Execution of computerized cognitive performance tests and polysomnography
- Quality control of study documents and data in readiness of Swissmedic monitoring

01.2013 – 09.2013 Clinical research associate, human sleep experiments
Center for Clinical Investigation, Harvard Medical School, Boston, USA

- Conductance of protocols to uncouple human circadian - behavioral rhythms
- Revision of clinical standard operating procedures
- Collection of biological samples
- Administration of computerized cognitive performance tasks
- Polysomnography

06.2012 – 12.2012 Clinical research associate, human sleep experiments
Centre for Chronobiology, University Psychiatric Clinics, Basel, Switzerland

Project: Effects of environmental noise on sleep quality, daytime sleepiness and cognitive performance in individuals with different variants of the *PER3*-gene

- Coordination and conductance of a scientific pilot study
- Development of study documents, such as study protocol, standard operating procedures, shift schedules and scientific presentations

- Revision of clinical documents for submission to ethics committees
- Recruitment of study participants
- Supervision of study staff members and training in clinical methods
- Polysomnography

07.2011 – 02.2012 Clinical research associate, human sleep experiments
Center for Clinical Investigation, Harvard Medical School, Boston, USA

Project: Validation of assessment tests and countermeasures for detecting and mitigating changes in cognitive function during robotics operations

- Supervision and drug administration of participants during simulated robotics tasks in space

01.2008 – 10.2009 Nutrition services coordinator
Nutrition and Food Services, Massachusetts General Hospital, Boston, USA

- Delivery of meals to patients in a cardiac intensive care unit and stepdown unit
- Quality control of patient meal preparation assembly line

CERTIFICATES IN CLINICAL RESEARCH

Methodology Good Clinical Practice (Clinical Trials Center, Zurich, Switzerland); Polysomnography (Harvard Medical School, Boston, USA)

SKILLS

Computer skills SAS; GraphPad Prism; Rembrandt Analysis Manager; DOMINO; MS Office

Languages English (native speaker); German (C2; DSH-Certificate, Leibnitz University, Hannover, Germany)

SUPERVISION OF JUNIOR RESEARCHERS

08.2018 – present Nora Krucker, B.Sc. Medicine, Master's Thesis
03.2019 – 06.2019 Maria Dimitriu, B.Sc. Biology, Semester's Thesis
05.2017 – 09.2019 Gioia Peterhans, B.Sc. Psychology, Master's Thesis
10.2018 – 07.2019 Zilla Huber, B.Sc. Psychology, Master's Thesis
03.2018 – 03.2019 Daniel Prossnitz, B.Sc. Psychology, Master's Thesis
07.2017 – 09.2017 Zora Kaiser, B.Sc. Medicine, Master's Thesis

AD HOC REVIEWER ROLE

06.2018 *Psychopharmacology, 236, pp. 1313–1322 (2019)*

TEACHING

05.2020 Lecture, An introduction to the autonomic nervous system and sleep – wake regulation, *Modul BME 306: Experimentelle Humanstudien Praktikum „Schlaf-Wach-Physiologie"*, University of Zurich, Zurich, Switzerland

02.2020 Workshop, Introduction to the methods of polysomnography, University of Zurich, Zurich Switzerland

05.2019 Workshop, Application of actigraphy; sleep scoring and artifacts; Assessment, statistical analysis and visualization of polysomnography and actigraphy datasets, *Modul BME 306: Experimentelle Humanstudien Praktikum „Schlaf-Wach-Physiologie"*, University of Zurich, Zurich, Switzerland

05.2016 Workshop, Sleep scoring and artifacts, *Modul BIO 406: Experimentelle Humanstudien, Teil „Schlaf-Wach-Physiologie"*, University of Zurich, Zurich, Switzerland

TALKS AT CONFERENCES

09.2017 Clinical Research Priority Project, *Retreat presentation,* Zurich, Switzerland: "Sleep and stress resilience"

02.2019 Dissertation Progress Report, Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland: “Sleep and resilience: investigation of sleep-wake behavior in a highly resilient study population”

12.2016 Clinical Research Priority Project, Sleep & Health Seminar, *Seminar presentation,* Zurich, Switzerland: “Sleep's role in the development and treatment of intrusive emotional memories”

PUBLICATIONS

Azza, Y., **Clark, I.**, Baur, D., Wilhelm, I., Müller, S., Karlen, W., Vetter, S., Seifrtiz, E., Landolt, H.-P., Kleim, B. (in preparation). Sleep’s role in the development of intrusive emotional memories and resilience after trauma.

Clark, I., Stucky, B., Azza, A., Müller, S., Karlen, W., Seifritz, E., Kleim, B., Landolt, H.-P. (2020, June). Shift work-related circadian disruption on diurnal rest-activity and sleep patterns in morning- and evening-type first responders under naturalistic conditions [abstract].

Stucky, B., **Clark, I.**, Azza, A., Müller, S., Karlen, W., Achermann, P., Kleim, B., Landolt, H.-P. (2020, June). Validation of a wearable heart rate and sleep tracker compared with polysomnography in police and rescue workers under natural settings [abstract].

Clark, I., Azza, Y., Müller, S., Schwab, P., Karlen, W., S., Seifrtiz, E., Kleim, B., Landolt, H.-P. (2018, September). A field-study on the role of sleep in stress resilience in rescue workers: preliminary analyses of wrist-actigraphy and home-polysomnography [abstract].

Clark, I., Azza, Y., Kaiser, Z., Müller, S., Karlen, W., S., Seifrtiz, E., Kleim, B., Landolt, H.-P. (2018, February). A field-study on the role of sleep in stress resilience in rescue workers: first preliminary analyses of polysomnographic data [abstract].

Clark, I., Landolt, H.-P. (2016). Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Medicine Reviews, 31, pp. 70-78 (2017)***.**

Clark, I., Brink, M., Tinguely G., Röösli, M., Probst-Hensch, N., Wunderli, J.-M., Pieren, R., Cajochen, C. (2014, September). Inter-individual differences in the effects of night-time noise exposure on sleep and cognitive performance during daytime [abstract].

Zurich, 16. December 2020