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Sleep microstructure: effects of nighttime noise exposure and age

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Abstract

Transient activation phases during sleep (i. e., cortical arousals, or autonomic arousals) are generally considered to fragment sleep and, as a result, negatively impact the recuperative value of sleep (Bonnet & Arand, 2003; Wesensten, Balkin, & Belenky, 1999). Transient activation phases can occur in response to external stimuli, such as transportation noise (Basner, Müller, & Elmenhorst, 2011); they also increase with ageing without external stimuli and are part of the normal aging process in humans (Bonnet & Arand, 2007; Mander, Winer, & Walker, 2017). Sleep spindles–spontaneous non-rapid eye movement sleep-related brain oscillations that also decline with ageing (Purcell et al., 2017)–modify external information processing and might serve as a physiological marker of sleep-related noise sensitivity (Dang-Vu, McKinney, Buxton, Solet, & Ellenbogen, 2010).

Twenty-six young (19-33 years, 12 women) and 16 older (52-70 years, 8 women) healthy volunteers underwent a repeated measures six-day laboratory study. Participants spent two noise-free nights (first and last night) and four transportation noise exposure nights (three nights with road and one with railway noise exposure in an incompletely counterbalanced sequence), two with continuous and two characterized by eventful noise (average sound levels of 45 dB, maximum sound levels between 50 and 62 dB for eventful noise). During the nights, polysomnography and body movements were recorded. Subjective sleep quality was assessed every morning and subjective sleepiness was assessed twenty times during scheduled wakefulness. Sleep staging and EEG arousal scoring followed standard criteria; sleep spindle characteristics and additional arousal response events (autonomic arousals and body movements) were identified by automatic detection algorithms.

In the older individuals, sleep was more fragmented under noise exposure compared to noise-free nights, while there were no effects on sleep macrostructure and all-night arousal and awakening rates in the young, which were independent of time-in-study effects. Arousal rate variation within NREM sleep cycles was best described by a u-shaped course with variations across cycles. Older participants had higher overall arousal rates than the younger individuals with differences for the first and the fourth cycle depending on the age group. During eventful noise exposure nights, overall arousal rates were increased compared to noise-free nights. Sleep spindle rates showed an age-related decline along with more noise-induced sleep alterations. Sleep structure and continuity were not differentially affected by noise exposure in individuals with a low versus a high spindle rate. For all investigated arousal response markers (cortical arousals, awakenings, autonomic arousals, and body movements), the probability of an event-related response during eventful road and railway noise exposure nights was significantly higher than spontaneous probabilities. Awakening and EEG arousal probability from single railway noise events depended on individual (e. g., age), acoustical (e. g., maximum sound pressure level and maximum slope of the sound pressure level), and situational factors (e. g., sleep stage, time of night), but was not affected by the all-night spindle rate.

Overall, the data suggest small effects of transportation noise exposure on sleep macro- and microstructure and a remarkable ability of the sleeping brain to adapt to nighttime noise. Sleep spindles are trait-like transitory EEG oscillations, which may reflect stable sleep but do not necessarily protect the sleeper against external stimuli such as nighttime transportation noise. Furthermore, when evaluating the effects of ageing and nighttime noise exposure on sleep fragmentation, the physiological microstructural evolution needs to be considered.

Contents

Chapter 1

Introduction & Theoretical background

On the behavioural level, sleep is characterised by a species-specific posture, prolonged behavioural unresponsiveness, elevated arousal threshold, but rapid reversibility of sleep with stimulation, and a rebound after sleep deprivation (Campbell & Tobler, 1984). Even if there is no ultimate answer to the question why we sleep, there is consensus that sleep is associated with restorative value for a variety of body functions (Krueger, Frank, Wisor, & Roy, 2016), such as the cardiovascular, metabolic, or immune system (Schmid, Hallschmid, & Schultes, 2015), and cognitive and emotional functioning (Alhola & Polo-Kantola, 2007; Basner, Rao, Goel, & Dinges, 2013; Diekelmann & Born, 2010; Gujar, McDonald, Nishida, & Walker, 2011).

During sleep the brain needs to perform a double task. On the one hand, there is the necessity to maintain sleep and isolate the organism from the constant flow of external information to unfold the full recuperative value of sleep, i. e., sleep stability. On the other hand, a certain degree of connection with its environment is necessary to allow for a quick reversibility of sleep when the organism is faced with physical threats, i. e., sleep fragility (Halasz, Bodizs, Parrino, & Terzano, 2014; Lecci et al., 2017). Sensory responsiveness during sleep mainly relies on auditory information and hearing might be "in the role of [a] watchman constantly on guard to signal danger" (Davis, Davis, Loomis, Harvey, & Hobart, 1939, p. 510). One example of the remarkable selectivity of auditory information processing during sleep is the anecdotal evidence of "Ammenschlaf", the quick reversibility of the mothers' sleep on signs of discomfort of their child (Zulley, 2018).

Nevertheless, auditory responsiveness also varies based on the sleep stage and the time of night. Some stages put the sleeping organism more than others in a vulnerable position. Given that the perception of sufficient safety is a requirement to unwind for sleep, some sort of protective field, defined as "an area of relative safety from external sources of danger, minimizing the chances for an intruder to go undetected" (Voss, 2004, pp. 35-36), needs to be established during sleep. Taking an evolutionary perspective, several strategies were developed that gave rise to the enormous differences in sleep duration and sleep patterns among species and may include: reduction of sleep duration; a polyphasic sleep pattern, where sleep occurs during several (non-)consecutive bouts (Capellini, Nunn, McNamara, Preston, & Barton, 2008); unilateral sleep, the alternating sleep between the two hemispheres, that can be observed in marine mammals (Cirelli & Tononi, 2008); or a social strategy, such as collective guarding behaviour observed in herd animals (Voss, 2004). In humans, vigilant monitoring might be reflected in the typical sleep architecture, characterized by sleep stage changes, regular occurrence of arousal responses during sleep, or the cyclic alternation between the two fundamental sleep

states non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Voss, 2001, 2004).

The close reflection on how we sleep is crucial for the understanding how transportation noise exposure and age affect sleep microstructure. The following parts will provide the reader with information on the fundamentals of sleep (first part) and on previous research on transportation noise effects on sleep (second part).

1 Sleep

The almost complete functional disconnection between brain and environment during sleep is the result of an inhibition of wake-promoting systems during sleep (Saper, Fuller, Pedersen, Lu, & Scammell, 2010; Takahashi, Kayama, Lin, & Sakai, 2010). Wake-promoting populations of neurons are primarily located within the ascending reticular activating system (ARAS), originating from the upper brainstem. They also reside, however, within the basal forebrain (Jones, 2003; Saper et al., 2010).

1.1 The ascending reticular activating system

The ARAS consists of two pathways of different origin, with different neuromodulators and a different temporal pattern of activity regarding waking, NREM, and REM sleep (see Figure 1.1). Two cholinergic cell groups in the mesopontine junction innervate the thalamus, primarily the relay nuclei, but also the intralaminar and reticular nuclei (Saper et al., 2010) and, in turn, modulate information flow to the cortex via thalamic gating (L. McCormick, Nielsen, Nicolas, Ptito, & Montplaisir, 1997). The monoaminergic cell groups in the upper brainstem and the caudal hypothalamus primarily project to hypothalamic areas, the basal forebrain, and the cerebral cortex, particularly the prefrontal cortex (Bar et al., 2016). In an ascending order, the monoaminergic system includes the following cell groups: the locus coeruleus, the raphe nuclei, the tuberomammillary nucleus, and the ventral periaqueductal grey matter (Saper et al., 2010; Tyree & de Lecea, 2017). Malfunctions and lesions in the ARAS cause profound sleepiness and were associated with encephalitis lethargica, the mysterious worldwide sleep sickness epidemic occurring between 1915–1927 (Dickman, 2001). Another group of neurons in the ventrolateral preoptic area (VLPO) in the anterior hypothalamus, using the inhibitory neurotransmitters galanin and GABA, shows specific activity during sleep (Sherin, Shiromani, McCarley, & Saper, 1996). The VLPO and the monoaminergic cell groups in the ARAS are reciprocally innervated (Saper et al., 2010). Maximum activity of the monoaminergic system during wakefulness inhibits the VLPO and maximum activity of the VLPO during sleep blocks the discharge of the monoaminergic cell groups: this mutual inhibition was described as a flip-flop switch, in analogy to electronic switches (Saper, Scammell, & Lu, 2005; Schwartz & Roth, 2008). This switch is further stabilized by orexin/hypocretin, a neuropeptide that is exclusively produced by a cluster of 50,000-80,000 neurons in the lateral hypothalamus (Thannickal et al., 2000). The loss of these neurons, as seen in narcolepsy (Thannickal et al., 2000), destabilizes the flip-flop

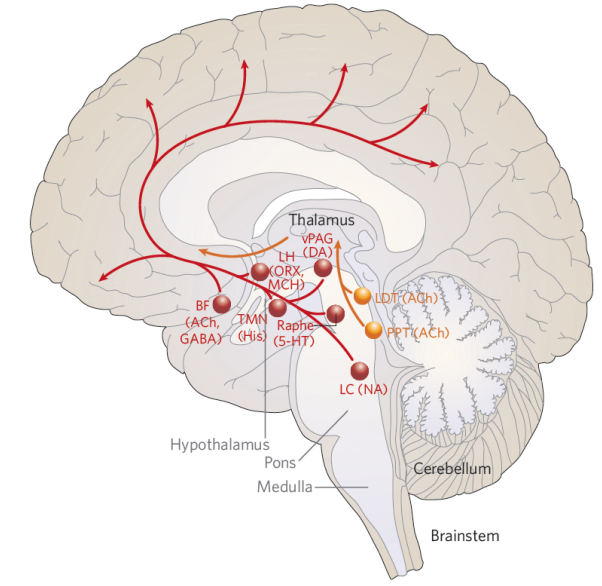

Figure 1.1: Schematic to describe the components of the ascending reticular activating system (ARAS) that is most active during wakefulness and the transition to wakefulness. Depicted are the cholinergic cell groups in orange and the monoaminergic cell groups in red. Acetylcholine (ACh) producing neurons, cholinergic neurons, reside within the pedunculopontine nuclei (PPT) and the laterodorsal tegmental nuclei (LDT). The monoaminergic cell group include: the noradrenergic (NA) locus coeruleus (LC), the serotoninergic (5-HT) raphe nuclei, the histaminergic (His) tuberomammillary nucleus (TMN), the dopaminergic (DA) ventral periaqueductal grey matter (vPAG), hypocretin (ORX) and melanin-concentrating hormone (MCH)-expressing cells in the lateral hypothalamus (LH), and the GABAergic (γ-aminobutyric acid) and cholinergic cell groups in the basal forebrain (BF). Adapted from Saper et al. (2005, p. 1258).

switch resulting in unstable patterns of wakefulness and sleep in narcoleptic patients that are characterized by hypersomnolence and imperative sleep during the day and by disrupted sleep episodes during the nighttime (American Academy of Sleep Medicine, 2014; Saper et al., 2010, 2005).

1.2 Sleep in the electroencephalogram

Sleep-related oscillatory brain activity, recorded using electroencephalography (EEG), can be grouped into two cardinal sleep rhythms: sleep spindles (11-15 Hz) and slow waves (0.75-4 Hz). Slow waves can be further split into delta activity (0.75-4 Hz) and slow oscillations (SO, 0.5-1 Hz; Dang-Vu, 2012; Dang-Vu et al., 2008; Steriade, 2006). SO, delta activity and spindle activity are evaluated using single events, visually or automatically identified from EEG recordings, or the use of power densities from spectral analysis techniques (the decomposition of the EEG signal in its constituent frequency components) as integrated measures of activity in the respective frequency range. While slow-wave activity (SWA) denotes power in the frequency range between 0.75-4.5 Hz, sigma activity refers to power in the frequency range between 11-15 Hz (Achermann, 2009). Typically, sleep recordings are derived from polysomnography (PSG) and include: EEG, electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). Windows of 30-s sleep recordings are visually assigned to sleep stages, either stage 1 NREM sleep (N1), stage 2 NREM sleep (N2), slow-wave sleep (SWS), or REM sleep according to standard scoring criteria of the manual published by the American Academy of Sleep Medicine (Berry et al., 2016). Spindles and K-complexes (KC), another large amplitude slow wave occurring either spontaneously or upon sensory stimulation during sleep (Halasz, 2016), are the

hallmark of N2. SWS is defined upon occurrence of SO or delta waves, occupying more than 20 % of a 30-s scoring window. Sleep macrostructure, the quantification of sleep stages, is build up by sleep microstructure, which includes the phasic events spindles, SO, the cyclic alternating pattern (CAP), or arousal responses as described below (Halasz & Bodizs, 2013).

1.3 Sleep spindles – waxing-waning waveforms during sleep

Neurons in the reticular thalamic nucleus (RT), a group of neurons that envelop the thalamus laterally, play a pacemaking role for spindle oscillations (Fuentealba & Steriade, 2005). This was inferred from the following observations: absence of oscillations in the spindle frequency range in the thalamocortical (TC)-circuitry when the TRN is separated from other thalamic neurons (Pare, Steriade, Deschenes, & Oakson, 1987) and presence of oscillations in the spindle frequency range in the deafferented TRN (Steriade, Domich, Oakson, & Deschenes, 1987). Figure 1.2 displays the complex functionality of the spindle generating circuitry composed of RT and TC neurons, located in the dorsal part of the thalamus. RT neurons activate TC neurons paradoxically. This activation was described as postinhibitory rebound burst of synaptic potentials: RT neurons inhibit the activity of TC neurons mediated by GABA; as a consequence, TC neurons are hyperpolarized and low-voltage gated T-type Ca^{2+} channels are deinactivated; which, in turn, promotes calcium spike activation (Astori, Wimmer, & Luthi, 2013; Beenhakker & Huguenard, 2009; Steriade, McCormick, & Sejnowski, 1993). Glutamatergic TC-RT collaterals reactivate RT neurons, which, in turn, paradoxically activates TC neurons again and results in the rhythmic sequence of RT and TC neuron burst discharges (Beenhakker & Huguenard, 2009). As TC neurons project to various cortical areas–core TC neurons project to cortical layers 4 and 6 and matrix neurons project to cortical layer 1 (Piantoni, Halgren, & Cash, 2016)–, this oscillatory activity is transferred to the cortex where excitatory postsynaptic potentials give rise to the spindle oscillation that can be recorded on the scalp (Dang-Vu, 2012; Steriade, 2003). The described thalamic circuitry is crucial, but the spindle event itself is network-generated within a corticothalamocortical circuitry (Steriade, 1999, 2006). When recorded on the scalp, spindle activity is most apparent at parietal and central EEG sites (De Gennaro, Ferrara, & Bertini, 2000) and have a preferred propagation pathway across the cortex as rotating waves from temporal, over parietal to frontal areas (Muller et al., 2016).

1.4 Sleep and aging

With aging, sleep undergoes alterations in duration, initiation, and maintenance (Mander, Winer, & Walker, 2017). Amounts of intra-sleep wakefulness, N1, and N2 increase, while amounts of SWS and REM sleep as well as total sleep time (TST) and sleep efficiency (SE) decrease with aging (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). However, the basic cyclic structure of sleep is largely preserved with aging so that age-related changes are especially evident in the sleep microstructure as indexed by an increase in sleep fragmentation and a

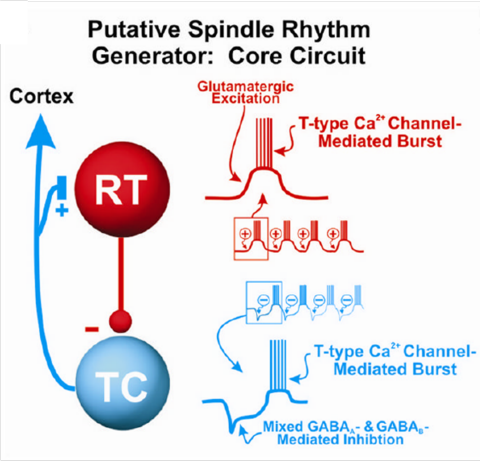

Figure 1.2: Presumed basic spindle generator based on two reciprocally connected groups of neurons. Neurons in the reticular thalamic nucleus (RT) inhibit the activation of excitatory thalamocortical neurons (TC), while postinhibitory rebound activity of TC cells reactivate RT neurons. T-type Ca^{2+} channel activity (depicted oscillations on the right) underlie RT and TC activity. Adapted from Beenhakker and Huguenard (2009, p. 614).

marked decline[1] in both SO and sleep spindles (Carrier et al., 2001; Landolt et al., 1996; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Purcell et al., 2017; Schwarz et al., 2017; Warby et al., 2014). The reported increase in sleep fragmentation might be due to the decreased ability to maintain consistent and stable sleep states with aging (Conte et al., 2014). Increased intra-sleep wakefulness is not associated with a decreased ability to re-initiate sleep but rather an increased number of awakenings: only 50 % of episodes of uninterrupted sleep last longer than nine minutes in the older, while in the young, 80 % of uninterrupted sleep episodes were longer than nine minutes (Klerman et al., 2013). The transformation of sleep parallels the concomitant neural network transformations with normative aging. Anatomical changes are often summarized as the result of a "shrinking brain", the age-related decline in gray and white matter (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Thambisetty et al., 2010). But, rates of decline vary with inter-individual characteristics, such as hypertension (Korf, White, Scheltens, & Launer, 2004; Raz et al., 2005) or pro-inflammatory genetic polymorphisms (Persson et al., 2014), as well as across brain regions. Medial temporal regions, including the hippocampus and adjacent areas, such as the entorhinal cortex, the prefrontal cortex, and the cerebellum are especially vulnerable to age-related gray matter decline (Fjell et al., 2009; Raz et al., 2010; Resnick et al., 2003). Loss in white matter integrity occurred across the whole brain (Resnick et al., 2003), but was especially marked in frontal and relatively low in temporal and posterior regions (Bartzokis et al., 2003; Salat et al., 2005).

[1] Also, it may well be that generation of SO and spindles is not reduced, but detection of single events or quantification using spectral analysis is impaired. Usually, the all-night absolute power density is reduced in older individuals (Carrier, Land, Buysse, Kupfer, & Monk, 2001; Landolt, Dijk, Achermann, & Borbély, 1996), which might be the result of an increase in conductance distance; i. e., grey matter decline and resulting increase in distance between the cerebral cortex and the scalp (Mander et al., 2014). Typically, amplitude thresholds, imposed on both manual scoring and automatic detection, are not adjusted to age. The standard scoring criteria published by the American Academy of Sleep Medicine, for example, require a 35 mV deflection of a slow wave to account for SWS scoring (Berry et al., 2016) which might result in reduced SWS in the presence of lower amplitude slow waves in older individuals.

1.5 Modelling how we sleep

Sleep is organized in 90-110 minutes ultradian cycles, which follow a characteristic and well-defined sleep architecture. A NREM descending-ascending complex is followed by a REM episode: the descending part is the first part of a NREM-REM cycle, when sleep progresses from lighter (N1) to deeper sleep (SWS) and the ascending part starts after the 'cycle turn', when sleep becomes more superficial and progresses towards REM sleep. Usually, 4-5 of those sleep cycles are completed over the course of one night (Feinberg & Floyd, 1979). Final awakening, when sleep is terminated spontaneously, preferentially occurs from REM sleep in young (Campbell, 1985; Murphy, Rogers, & Campbell, 2000), but not in older individuals (Dijk, Duffy, & Czeisler, 2001; Murphy et al., 2000).

Classically, two distinct processes are used to model the timing, duration, and quality of sleep: a homeostatic and an endogenous circadian process, in combination referred to as the Two-Process model of sleep regulation (Borbély, 1982; Daan, Beersma, & Borbély, 1984). In short, the circadian process delineates a near 24-h periodicity in physiology, driven by a circadian pacemaker that is invariant to sleep or wakefulness states and promotes wakefulness during the species-specific waking period and sleep during the sleeping period (Borbély, 1982). Sleep homeostasis (as reviewed in Achermann & Borbély, 2017) denotes the basic principle "the longer we are active (and, perhaps, the more we are active), the deeper our sleep [or: the higher our sleep pressure]" (Daan et al., 1984, p. R161). A process is regulated sleep homeostatically, if it is affected by modulations in sleep pressure as it occurs after sleep deprivation or within a sleep episode when sleep pressure dissipates across sleep cycles. In general, SWA or the amount of SWS are validated electrophysiological markers of the homeostatic process or sleep pressure (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981).

During recovery sleep after sleep deprivation, spindle activity is usually reduced as demonstrated for the number of individual spindles (Dijk, Hayes, & Czeisler, 1993) and the power density in the spindle frequency range (Borbély et al., 1981), while SWA is usually increased, especially during the first two sleep cycles (Dijk, Brunner, & Borbély, 1990; Dijk et al., 1993). Spindle rates linearly increase across successive sleep cycles (Dijk & Czeisler, 1995; Guazzelli et al., 1986; N. Martin et al., 2013; Purcell et al., 2017; Wei, Riel, Czeisler, & Dijk, 1999), while SWA is maximal during the first cycle and linearly declines across successive cycles (Achermann & Borbély, 1997; Cajochen, Pischke, Aeschbach, & Borbély, 1994; Dijk et al., 1993). Using the Two-Process model, SWA rebound and spindle activity after sleep deprivation as well as sleep regulation across successive sleep cycles can be modelled, but how we sleep–the characteristic temporal evolution of EEG rhythms during the NREM descending-ascending complex and subsequent REM sleep–cannot be addressed with this framework and the underlying mechanisms remain elusive (Phillips, Robinson, & Klerman, 2013).

Within sleep cycles, the spindle and SWA time-courses evolve inversely (see also Figure 1.3): while spindle activity has a u-shaped pattern, SWA largely follows a reversed u-shaped pattern (Aeschbach & Borbély, 1993). Each cycle can be subdivided into three parts: during the first part of a cycle, spindle activity exhibits a steep increase, while SWA is only gradually

building up; during the second part of a cycle, which is mainly determined by a distinct peak in SWA, spindle activity shows a concomitant local through; after another short increase in spindle activity, SWA and spindle activity sharply decrease in parallel during the transition to REM sleep during the last part (Dijk et al., 1993; Purcell et al., 2017; Uchida, Atsumi, & Kojima, 1994). The slope of spindle activity and SWA increases during the first part of the cycle and this rise rate declines gradually across sleep cycles (Dijk et al., 1990, 1993). This characteristic within-cycle relationship between spindle activity and SWA is due to the progressive hyperpolarization of TC neurons, which underlies these EEG events: the increase in hyperpolarization leads to spindles that give rise to slow waves when TC neurons are in an even more hyperpolarized state (Merica & Fortune, 2003; Steriade et al., 1993).

The neuronal transition probability (NTP) model suggests a 3-element cascade process, including EEG rhythms in the delta, sigma, and beta range (16-31 Hz) (Merica & Fortune, 2011). As depicted in Figure 1.3, in the 'sleep towards' phase (resembling the descending part of the cycle as described earlier), EEG dynamics follow a beta-sigma-delta pattern: during the quasi-exponential decay of beta, both sigma and delta power rise with an early peak of sigma power and a subsequent peak of delta power; during the 'sleep away' phase after the 'switch point' (resembling the ascending part of the cycle), the reverse pattern occurs towards REM sleep: a delta-sigma-beta direction with a rapid decline in delta power, a second peak in sigma power and a sharp increase in beta power (Merica & Fortune, 2011). The elegance of this model is that it includes a subcortical process (and with it the ARAS) in a model for sleep regulation: the progressive increase in VLPO firing during sleep (and during the sleep onset period) induces a decrease in brainstem firing rates which results in diminished thalamic input, which, in turn, might give rise to the progressive hyperpolarization of TC neurons (Merica & Fortune, 2003).

1.6 Disruption of sleep continuity

Sleep is not a stable, but a dynamic process (Halasz & Bodizs, 2013). Transient phases of activation disrupt the continuity of sleep as it becomes evident in desynchronizations of EEG rhythms, "a rapid shift from high-amplitude low-frequency EEG activity, typical of sleep, to low amplitude high-frequency EEG activity, typical of wakefulness" (Halasz, Terzano, Parrino, & Bodizs, 2004, p. 2), or variations in autonomic nervous system functions, such as alterations in cardiac activity, respiration, or body movements (Penzel et al., 2016). These phases of vigilance fluctuations are so-called arousal (Bonnet et al., 1992), "a temporary intrusion of wakefulness into sleep" (Halasz et al., 2004, p. 3). The term arousal has two meanings in the literature (see also Trinder, Waloszek, Woods, & Jordan, 2012). In general, the term arousal is used to describe a change of cortical activity from a lower to a higher level with increased alertness and attention (Trinder et al., 2012). Arousal responses during sleep, however, are transient events with a clear on- and offset–a relative phenomenon with an increase in activity compared to a pre-event/-state baseline (Halasz et al., 2004). Arousal are considered an integral and essential characteristic of the course of physiological sleep (Akerstedt et al., 2002; Bonnet & Arand, 2007; Halasz et al., 2004). They can occur in response to external or internal stimuli and might also include signals

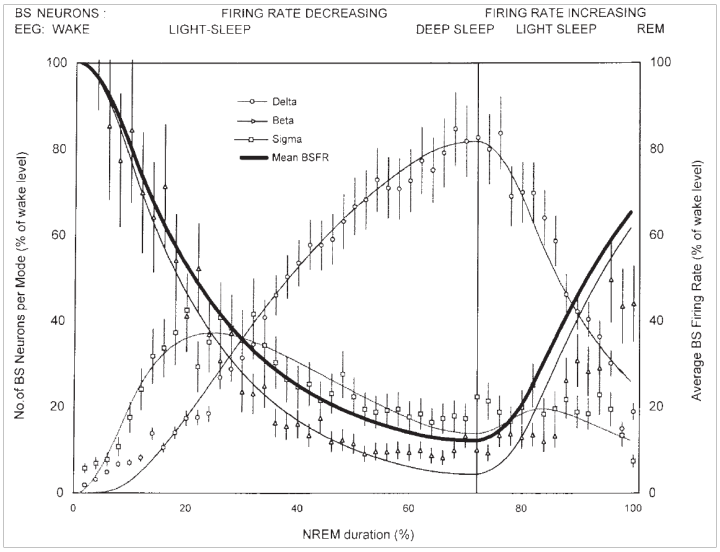

Figure 1.3: Time courses of the spectral power in the delta, beta, and sigma frequency range during the first sleep cycle, averaged over six individuals. Error bars represent the standard error of the mean. The evolution of the mean brainstem firing rate (BSFR) was calculated as weighted average of delta, beta, and sigma powers at any given point in time according to the neuronal transition probability (NTP) model. Adapted from Merica and Fortune (2003, p. 1045).

that are not part of a standard PSG, such as intestinal passage or organ dysfunction (Halasz et al., 2004). Consequently, arousals are common in sleep-related disorders, such as sleep-disordered breathing, as obstructive sleep apnea syndrome (OSAS; Chugh, Weaver, & Dinges, 1996; Poyares, Guilleminault, Rosa, Ohayon, & Koester, 2002), or periodic limb movement disorder (PLMD), but also in response to other internal or environmental sleep-disturbing factors, such as noise (i. e., snoring of a bed partner, neighbourhood or transportation noise, etc.), or pain (Lavigne et al., 2000). In the following, several arousal response markers are described in detail: autonomic arousal, cortical arousal, short and longer EEG awakenings. The naming of the marker refers to the originating subsystem: the autonomic nervous system is primarily activated during autonomic arousal, while it is the cortex during cortical arousal reactions.

Cortical arousal

The agreement on definition and scoring of single cortical arousal reactions during sleep is only ostensible so that a multitude of definitions is used in the literature (Halasz et al., 2004). Figure 1.4 depicts exemplary polysomnographic traces of four different groups of cortical arousal reactions. The most established definition is given by the American Sleep Disorders Association (ASDA) (Bonnet et al., 1992) and serves as “a quantifiable biological marker for sleep disturbance” (Hirshkowitz, 2002, p. 203). ASDA arousals are defined as “an abrupt shift in EEG frequency, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles” for at least 3 seconds (Bonnet et al., 1992, p. 174). When occurring during REM sleep, a concomitant 1-s increase in submental EMG amplitude is required. Another influential, more detailed and comprehensive definition for cortical arousal reactions during sleep is the one

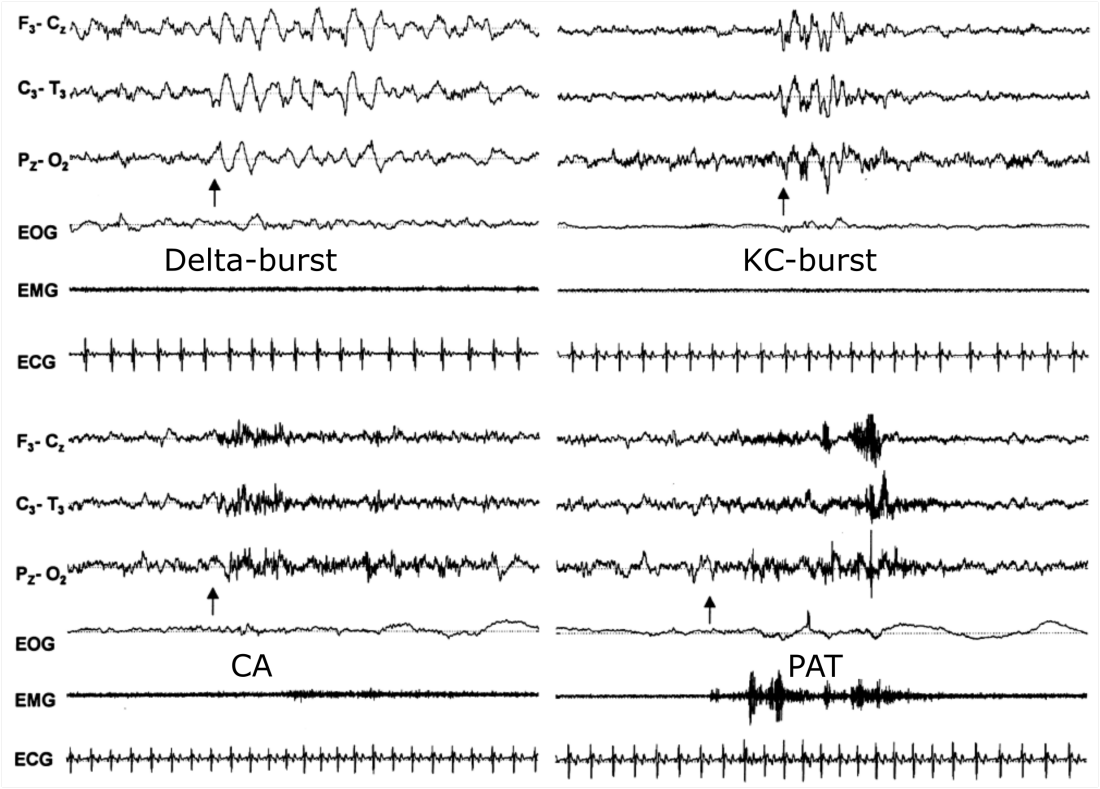

Figure 1.4: Exemplary polysomnographic traces of four different groups of cortical arousal reactions. The arrows depict the onset of individual reactions. Delta-bursts are trains of delta waves that are clearly distinguishable from the background activity. KC-bursts denote a sequence of two or more K-complexes (KC). ASDA arousal (CA) and phases of spontaneous transitory activity (PAT) were scored according to definitions given in the text. Note the increases in heart rate (ECG) and muscular tone (EMG) accompanying the EEG desynchronizations for CA and PAT. Whether delta- and KC-bursts are true cortical arousal reactions is still a matter of debate (Halasz et al., 2004; Sforza, Jouny, & Ibanez, 2000). Adapted from Sforza et al. (2000, p. 1613).

provided by the Strasbourg School, the "phases d'activation transitoire" (PAT) (Schieber, Muzet, & Ferriere, 1971). PAT are characterized by an acceleration of EEG background activity (i. e., disappearance of delta waves and spindles, as well as appearance of alpha and beta activity) in association with autonomic (i. e., transient increase in heart rate (HR)) and muscular activation (i. e., transient increase in muscular tone, limb movement, or changes in posture); and by the occurrence of transient alpha activity or transient disappearance of rapid eye movements during REM sleep (Halasz et al., 2004; Schieber et al., 1971; Sforza, Chapotot, Pigeau, & Buguet, 2008). Consequently, evaluating cortical arousal reactions according to the PAT definition results in a lower number when compared to an evaluation according to the ASDA definition, which is mainly defined by EEG desynchronizations (Sforza et al., 2008; Sforza, Chapotot, Pigeau, Paul, & Buguet, 2004).

In the following, only ASDA arousal, as the most established EEG arousal marker, will be considered and will be termed cortical arousal (CA). During undisturbed, physiological sleep, the average number of CA is 10.6-16.8 per hour of TST in young individuals, 18-40 years of

age (Bonnet & Arand, 2007; Boselli, Parrino, Smerieri, & Terzano, 1998; De Gennaro, Ferrara, & Bertini, 2001; Sforza et al., 2008, 2004) and increases with aging (Bonnet & Arand, 2007; Boselli et al., 1998; Terzano, Parrino, Rosa, Palomba, & Smerieri, 2002). CA do not seem to increase across the night (De Gennaro et al., 2001; Sforza et al., 2008) and appear more often in the ascending than the descending part of the sleep cycle (Halasz et al., 2004; Terzano, Parrino, Boselli, Smerieri, & Spaggiari, 2000). During recovery sleep following total sleep deprivation, CA rates were reduced (Sforza et al., 2004), particularly during NREM sleep (De Gennaro et al., 2001).

Autonomic arousal

Autonomic arousals (AA), isolated transient subcortical increases in sympathetic nerve activity, were primarily analyzed in the field of sleep-disordered breathing (Adachi et al., 2003; Raymond, Cayton, & Chappell, 2003) using ECG markers, such as variations in HR (Griefahn, Brode, Marks, & Basner, 2008; Togo, Cherniack, & Natelson, 2006; Trinder et al., 2003) or respiration (Carley, Applebaum, Basner, Onal, & Lopata, 1997), but also other autonomic markers, such as pulse transit time (Pitson & Stradling, 1998; Stradling, Barbour, Glennon, Langford, & Crosby, 2000), blood pressure (Davies, Belt, Roberts, Ali, & Stradling, 1993; Shahrbabaki, Ahmed, Penzel, & Cvetkovic, 2017), or peripheral markers, such as skin vascular conductance, approximated using the finger pulse wave amplitude (Catcheside, Chiong, Mercer, Saunders, & McEvoy, 2002). Methodologically, sympathetic activation can be measured in relation to other events (e. g., leg movements, respiratory events, CA, or external stimuli, such as noise) as a relative increase in heart rate variability (HRV) compared to a pre-event baseline (Azarbarzin, Ostrowski, Hanly, & Younes, 2014; Goff, O'Driscoll, Simonds, Trinder, & Morrell, 2008; Griefahn, Brode, et al., 2008; Sforza et al., 2000; Togo et al., 2006; Winkelman, 1999; Yang, Jordan, White, & Winkelman, 2006) or purely based on HRV using rule-based classification with fixed thresholds (Basner, Griefahn, Müller, Plath, & Samel, 2007) or machine learning approaches (Olsen et al., 2018). Consequently, AA often coincide with CA (AA-CA+), awakenings, or body and leg movements, but they also occur in isolation (Basner et al., 2007; Olsen et al., 2018; Shahrbabaki et al., 2017; Togo et al., 2006). A characteristic HR morphology was noticed for AA-CA+, an initial HR increase, followed by a HR decrease: a tachycardia-bradycardia complex (Schieber et al., 1971; Sforza et al., 2000; Togo et al., 2006; Trinder et al., 2003). Usually, AA precede the onset of CA by 1-10 beats (Bonnet & Arand, 1997; Sforza et al., 2000; Togo et al., 2006). AA intensity is proportional to both CA duration (Basner et al., 2007; Trinder et al., 2003) and CA intensity (Azarbarzin et al., 2014; Sforza et al., 2000). While NREM AA-CA+ were associated with increases in the delta, theta, alpha, and beta frequency bands, which is in agreement with the ASDA scoring rules for CA, delta frequency power was increased for NREM AA-CA-, which most likely represents single or bursts of KC or SO (Togo et al., 2006). Consequently, both SO- and KC-bursts were associated with HR increases even when these increases were smaller in magnitude when compared to CA (Sforza et al., 2000, see also Figure 1.4). Phases with SO- and KC-associated HRV elevations were also termed subcortical arousal as typically no overt EEG desynchronization is observed (S. E. Martin, Engleman, Deary, & Douglas, 1996; Sforza

et al., 2000). In fact, the functional significance of KC was debated for a long time (Colrain, 2005) and can be best described as Janus-faced (Halasz, 2016) exhibiting both arousal-like (Church, Johnson, & Seales, 1978; Ehrhart, Ehrhart, Muzet, Schieber, & Naitoh, 1981; Jahnke et al., 2012; Johnson & Karpan, 1968; Sforza et al., 2000), as well as sleep-promoting features (Bastien et al., 2009; Wauquier, Aloe, & Declerck, 1995).

Awakening

Awakening from sleep is mainly defined based on EEG signals as reoccurrence of alpha rhythm and/or low voltage, mixed frequency EEG activity, accompanied by high EMG tone, and/or rapid eye movements or eye blinks for more than 15 seconds (Berry et al., 2016). Behaviorally, it can be defined as the moment in time individuals press a button whenever they awake from sleep (called signalled awakening). However, not every EEG-verified awakening is associated with recovery of full consciousness of the sleeper. Both conscious awareness of being awake during sleep and the next-morning recollection of it was demonstrated to depend on the awakening duration. A minimum duration of approximately two minutes was suggested (Campbell & Webb, 1981; Vallat et al., 2017). Usually, individuals are amnestic for brief, shorter than two minutes lasting awakenings during the night, sometimes, as common experience suggests, even though consciousness was regained and goal-directed actions such as talking took place. This phenomenon resembles the amnesia for stimuli presented prior to or during the sleep onset phase–termed mesograde amnesia to characterize its status between anterograde and retrograde amnesia (Wyatt, Bootzin, Allen, & Anthony, 1997; Wyatt, Bootzin, Anthony, & Bazant, 1994)– or stimuli presented after awakening from SWS (Bonnet, 1983). In the same vein, successive awakening reactions, separated by only few minutes of sleep, might subjectively be perceived as only one. Consequently, the number of EEG-verified, objective awakenings is higher than the next-morning self-reported number of awakenings (Baker, Maloney, & Driver, 1999; Ohayon, Krystal, Roehrs, Roth, & Vitiello, 2010).

During undisturbed, physiological sleep, the average number of EEG-verified awakenings is 3-4 per hour/TST in young individuals, 18-40 years of age (Bonnet & Arand, 2007) and the majority of awakenings is usually brief (i. e., $<$ 1 min) (Goldenberg, Goldenberg, Lacombe, & Benoit, 1981; Vallat et al., 2017). Both all-night intra-sleep wakefulness and number of awakenings increase with aging (Bonnet & Arand, 2007; Dijk et al., 2001; Klerman et al., 2013; Landolt et al., 1996). Time spent in intra-sleep wakefulness increases across sleep cycles in middle-aged (57-64 years) but not younger individuals (Landolt et al., 1996). The probability of awakenings is usually highest at the beginning of a sleep cycle (i. e., after the end of a REM sleep episode), increasing across the night; but, occasionally, awakenings occur at random times (Akerstedt et al., 2002; Merica & Gaillard, 1986; Schulz & Bes, 1998). In general, both the duration of intra-sleep wakefulness (Borbély et al., 1981) and the number of intra-night awakenings are reduced after total sleep deprivation (Bonnet, 1986; De Gennaro et al., 2010).

1.7 Arousal: from the brainstem to the cortex

Neurophysiologically, arousal responses during sleep are generated within the brainstem-ARAS-thalamus-cortex circuitry. The brainstem-ARAS part was exclusively examined in rodents using experimental lesions, injections of pharmacological antagonists, or optogenetics (M. E. Carter et al., 2010; Tyree & de Lecea, 2017), whereas the thalamus-cortex part was also assessed in humans (Peter-Derex, Magnin, & Bastuji, 2015). Activations of the ARAS precede the sleep-to-wake transition as demonstrated for the locus coeruleus (M. E. Carter et al., 2010) or the dorsal raphe nuclei (Cho et al., 2017), and modulate sensory responsiveness during sleep, as demonstrated by transient increased discharge rates in response to auditory, alerting stimuli (Cho et al., 2017; Fulcher, Phillips, & Robinson, 2008; Takahashi et al., 2010). Further evidence for the involvement of the ARAS neuronal populations in activation during sleep stems from H1R knockout mice, i. e., mice lacking H1 receptors for histamine. They showed less sleep stage changes and CA (here, wakefulness < 15 s) than mice with intact H1 receptors (Huang et al., 2006). In humans, CA were preceded and accompanied by a significant decrease in all EEG frequency bands on the thalamic level (delta, theta, alpha, sigma, and beta), stereotyped for both N2 and SWS CA; during REM CA, all EEG frequency bands but beta were significantly reduced (Peter-Derex et al., 2015). Interestingly, KCs, discussed in the literature with respect to their arousal- and/or sleep-promoting functions, are also associated with brainstem and thalamic activations (Jahnke et al., 2012). On the cortical level, however, activation patterns were less stereotypical. CA during SWS were associated with decreases in delta and/or sigma power or paradoxical high-amplitude rhythmic slow-wave activity (Peter-Derex et al., 2015). During N2 sleep, cortical activation was even more variable: depending on the recording site, CA were associated with both increases and decreases of slow and/or fast rhythms, with sigma activity reduction as the most consistent finding (Peter-Derex et al., 2015). CA heterogeneity was also reported by others (Nobili et al., 2011). In addition, they observed the coexistence of EEG desynchronizations in one (motor cortex) and sleep-like EEG features in other cortical areas (such as frontal areas) suggesting that CA are not an all-or-nothing phenomenon and that they also occur locally (Nobili et al., 2011). CA are not short awakenings, but rather an in-between state with thalamic and cortical activations being different (for N2 sleep) or in-between (for SWS) those activation patterns observed during wakefulness and sleep (Peter-Derex et al., 2015). Nevertheless, CA and awakenings share the underlying activation of the wake-promoting circuitry, but TC and RT depolarizations–naturally occurring at the transition from sleep to wake (D. A. McCormick & Bal, 1997)–might be insufficient during CA to induce a full-blown awakening (Foo & Mason, 2003; Halasz, 2016; Kato, Masuda, Yoshida, & Morimoto, 2011; Leung & Mason, 1999). It was suggested that arousal responses are organized hierarchically (Halasz, 1998; Halasz et al., 2004; Sforza et al., 2000). This hierarchy, a ranking of elements from the lowest to the highest, can be interpreted at least with respect to four different aspects: intensity/duration, frequency of occurrence, repercussion on recuperative value of sleep, and responsiveness to sensory stimulation (see also Chapter 5).

1.8 Repercussions of sleep fragmentation

Sleep disruption impairs the restorative value of sleep (Stepanski, 2002; Wesensten et al., 1999) which might be mediated by the arousal response marker (Chugh et al., 1996). Experiments disrupting sleep using acoustical stimulation of various durations and intensities with both regular and irregular intervals during sleep observed that sleep disruption increases homeostatic sleep pressure. Participants showed reduced sleep latencies during subsequent daytime napping, which indicates increased daytime sleepiness (Bonnet, 1986; S. E. Martin et al., 1996; S. E. Martin, Wraith, Deary, & Douglas, 1997; Philip, Stoohs, & Guilleminault, 1994; Roehrs, Merlotti, Petrucelli, Stepanski, & Roth, 1994), as well as an impairment of cognitive and emotional functioning (Downey & Bonnet, 1987; S. E. Martin et al., 1996, 1997). While an increase in CA due to acoustical stimulation resulted in a decrease in next-day cognitive performance, this could not be demonstrated for AA (Guilleminault, Abad, Philip, & Stoohs, 2006; S. E. Martin et al., 1996, 1997). However, sleep staging and sleep disruption are interrelated, as per definition, CA leads to a sleep stage change, usually to N1 sleep (Berry et al., 2016). As a result, there is no clear evidence whether the disruption-induced increase in time spent in N1 sleep or reduced TST in case of awakenings (Bonnet, 1989; S. E. Martin et al., 1996; Philip et al., 1994; Roehrs et al., 1994) or sleep disruptions per se impacted on the restorative value of sleep (Wesensten et al., 1999).

1.9 The depth of sleep

Very early in sleep research, attempts have been made to define the depth of sleep. Traditionally, auditory arousal thresholds have been assessed, i. e., the sound intensity of an auditory stimulus that is required to elicit a reaction in the sleeping individual, typically in the form of an awakening but later also in the form of an EEG arousal. In the following, this threshold is mostly referred to as auditory responsiveness, the exact opposite meaning of threshold. As early as in 1863, Ernst Otto Heinrich Kohlschütter, a student of the well-known physicist and experimental psychologist Gustav Theodor Fechner, published the first systematic investigation on the depth of sleep. He studied one participant during eight consecutive nights. He used an auditory stimulus to disrupt sleep, namely "a pendular hammer hitting a thick slate slab" (Basner, 2010, p. 418), attempting to arouse the participant every 30-60 minutes throughout the sleep period. He increased the stimulus intensity step-wise, using six stimuli of the same intensity, respectively, until he noticed a "sign of awakening in the sleeper"[2] (Kohlschütter, 1869, p. 216). Auditory responsiveness steeply decreased after sleep onset with the lowest all-night auditory responsiveness around one hour after sleep onset, and steeply increased again until approximately two hours after sleep onset; the remaining night was characterised by progressively increasing auditory reactivity with signs of ultradian variations (Basner, 2010; Kohlschütter, 1869).

[2] In the absence of electrophysiological methods–the EEG was only established around 1929 by Hans Berger–Kohlschütter closely observed the sleeper, sitting next to the bed all night, and evaluated respiration depth, frequency, and regularity, as well as body movements to approximate sleep and wakefulness. Additionally, the existence of REM was only firmly established around 1955 by the University of Chicago sleep group lead by Nathanial Kleitman (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957).

Since then, a multitude of experiments assessed auditory responsiveness during sleep. Most of them aimed at characterizing depth of sleep, but some were primarily interested in dreaming mentation upon serial awakening from sleep, reporting on auditory responsiveness on the side (Feige et al., 2018; Goodenough, Lewis, Shapiro, & Sleser, 1965; Zimmerman, 1970). In general, responsiveness decreased across NREM states and was lowest during SWS, as demonstrated for awakening probability and threshold in dB (Busby, Mercier, & Pivik, 1994; Goodenough et al., 1965; Philip et al., 1994; Rechtschaffen, Hauri, & Zeitlin, 1966; Zimmerman, 1970) as well as for CA probability (Kato, Montplaisir, & Lavigne, 2004; Roehrs et al., 1994). Results were inconsistent with respect to the question whether auditory responsiveness differed between SWS and REM sleep (Rechtschaffen et al., 1966; Roehrs et al., 1994; Williams, Hammack, Daly, Dement, & Lubin, 1964). However, a higher responsiveness during tonic as compared to phasic REM sleep (Ermis, Krakow, & Voss, 2010) and less variability in response to different stimuli during REM compared to NREM sleep (Buxton et al., 2012) were suggested. Intra-night variations depended on sleep stage distributions and the applied number of acoustical stimuli, so that, consequently, reported relationships between responsiveness to auditory stimuli and time of night are not univocal: some demonstrated an increase in responsiveness across the night (Ferrara, De Gennaro, Casagrande, & Bertini, 1999; Keefe, Johnson, & Hunter, 1971; Rechtschaffen et al., 1966; Watson & Rechtschaffen, 1969), others a decrease (Harsh et al., 1987; Philip et al., 1994; Roehrs et al., 1994; Williams et al., 1964), while one experiment demonstrated a curvilinear pattern (Bonnet & Johnson, 1978), which might be further moderated by circadian processes, as indicated by the core body temperature (Lammers, Badia, Hughes, & Harsh, 1991). Additionally, responsiveness to auditory stimuli during sleep depends on the characteristics of the stimulus, mainly the SPL, but also the meaning and significance of stimuli (Voss, 2010). However, certain questions remain unanswered, as for example why some stimuli induce CA and others a full-blown awakening, or whether inter-individual auditory processing differences exist that determine the activation preference on the activation hierarchy upon acoustical stimulation.

After SWS manipulation, responsiveness to auditory stimuli was reduced as compared to baseline conditions as indexed by an increase in dB required to elicit an awakening from 49 to 63 dB during nights following selective SWS suppression (Ferrara et al., 1999) or from 53 to 67-70 dB during nights following 40-64 h total sleep deprivation (Rosa & Bonnet, 1985). The decrease in auditory responsiveness parallels the SWS increase (i. e., the increase in homeostatic sleep pressure) generally observed during recovery sleep following sleep deprivation, referred to as SWS rebound (Borbély et al., 1981). Similarly, differences in homeostatic sleep pressure, approximated by habitual daytime sleepiness, were demonstrated to differentially modify responsiveness to auditory stimulation: responsiveness increased between the first and the second part of the night in alert individuals (i. e., low habitual daytime sleepiness, sleep latency $\geq$ 10 min during daytime napping), but remained stable across the night in sleepy individuals (i. e., high habitual daytime sleepiness, sleep latency $\leq$ 5 min during daytime napping) (Rosenthal et al., 1996). Moreover, responsiveness to auditory stimulation exhibits a striking ontogenetic variation. In children (5-7 years of age) and preadolescents (8-12 years of age), 57 % (45 %

for preadolescents) of all-night awakening attempts with sound intensities as high as 120 dB were unsuccessful (Busby et al., 1994). This was very different from young adults (20-24 years of age) who were awakened upon every attempt and with much lower sound intensities: 102-112 dB in children and preadolescents and 68 dB in young adults (Busby et al., 1994). The difficulty to awaken children and preadolescents during sleep parallels the high amount of SWS and the low number of spontaneous CA in this age group as compared to mature adolescents, respectively (Kurth et al., 2010).

1.10 Basic auditory information processing during sleep

In general, auditory information processing as assessed by means of average event-related potentials is decomposed in early-, mid-, and late-latency event-related electrical potential (ERP) components (i. e., in time after auditory stimulus onset). Mid-latency components are sensitive to modulations in vigilance states and include the P1-N1-N2 complex: peak latencies at approximately 50, 100 and 200 ms reflect processing in primary and higher-order auditory cortices as well as higher-order cognitive processes (Atienza, Cantero, & Escera, 2001; Colrain & Campbell, 2007). During NREM sleep, the N1 ERP demonstrates a gradual amplitude decrease during the deepening of sleep and P2 is usually increased in amplitude, indicating altered auditory information processing during sleep (Cote, Epps, & Campbell, 2000; Harsh, Voss, Hull, Schrepfer, & Badia, 1994; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Schabus et al., 2012). P2 was further increased when very brief stimuli (typically, stimulus duration of 55-300 ms) were presented during sleep spindles (Elton et al., 1997). This was, however not conclusively shown (Cote et al., 2000; Schabus et al., 2012). Additionally, auditory information processing during sleep was investigated using variations in blood oxygenation level dependent (BOLD) signals. At an early stage of auditory information processing (i. e., thalamus and primary auditory cortex), the BOLD signal increases associated with auditory stimulation were similar during sleep and wakefulness (Dang-Vu et al., 2011; Portas et al., 2000; Schabus et al., 2012), but lower in higher-order auditory areas (Portas et al., 2000). However, processing was modulated by transient NREM EEG events: tones delivered during sleep spindles were not associated with significant BOLD signal increases in the thalamus and the primary auditory cortex as compared to spindle asynchronous tones (Dang-Vu et al., 2011); BOLD signal increases in higher-order auditory areas were higher during the up- as compared to the down-phase of slow oscillations (Schabus et al., 2012); and, BOLD signal decreases at all stages of auditory information processing correlated positively with number of induced KCs (Czisch et al., 2004). It has been hypothesized that TC cell firing during spindles gates afferent signaling to the cortex (Steriade, 2006) in order to isolate the cortex from environmental throughput–a function described as “thalamic gating”. Consequently, sleep spindles might act to physiologically protect sleep. Indeed, it was demonstrated that individuals with higher all-night spindle rates had a lower hazard ratio of sleep disruption due to environmental noise (i. e., higher auditory arousal thresholds) than individuals with a lower all-night spindle rate (Dang-Vu et al., 2010). In general, sleep spindles are implicated in learning, memory consolidation and plasticity

processes (as reviewed in Rasch and Born (2013) and Astori et al. (2013)) and are considered as physiological markers of intelligence or cognitive abilities in general (Fogel & Smith, 2011; Schabus et al., 2006). Consequently, the two spindle functions might be interrelated: sleep protection might enable off-line memory consolidation and plasticity processes (Dang-Vu, 2012).

1.11 Preliminary summary

All things considered, arousal responses are an integral and essential characteristic of the course of physiological sleep (Akerstedt et al., 2002; Bonnet & Arand, 2007; Halasz et al., 2014, 2004). Both, physiological arousal responses and responsiveness to auditory stimulation evolve in parallel with the temporal progression of SWS (and hence sleep pressure), within and across sleep cycles (Akerstedt et al., 2002; Halasz et al., 2004; Merica & Gaillard, 1986; Schulz & Bes, 1998; Terzano & Parrino, 2000; Terzano et al., 2000) and are reduced with homeostatic sleep pressure manipulation, such as sleep deprivation. There is consensus that the increased number of arousal responses seen in sleep disorders, such as OSAS, impairs sleep recuperative functions and leads to excessive daytime sleepiness or cognitive impairments, but the cutoff between normal and abnormal values has not yet been determined (Berry et al., 2015). In essence, recurring arousal responses can be considered as guardians of sleep (as suggested in Parrino & Vaudano, 2018): they provide a low-level of information processing during sleep (Jahnke et al., 2012) and allow to quickly proceed with sleep when the sleep environment is considered safe. And, transient arousal responses are also guardians of life: they allow to quickly reverse sleep and to act accordingly in the face of internal or external threats to the sleeping organism (Nobili et al., 2011; Voss, 2001). In OSAS for example, transient activations rehabilitate normal breathing by clearing obstructed airways and eliminating hypoxemia caused by apnea or hypopnea (Edwards et al., 2010). In addition, arousal responses during sleep (including EEG arousal or an increase in sympathetic nerve activity) might be a critical in-between brain state, which can provoke other sleep-related paradoxical activity, such as rhythmic masticatory muscle activity seen in sleep bruxism (Huynh et al., 2006; Lavigne et al., 2007) or nightly seizures and epileptoform EEG signatures, such as spike-wave discharges (Halasz, Kelemen, & Szucs, 2013; Parrino, Smerieri, Spaggiari, & Terzano, 2000), as demonstrated specifically for PLMD-induced arousal and seizure rate (Voges & Stodieck, 2017) or OSAS-induced arousal and seizure rate (Chihorek, Abou-Khalil, & Malow, 2007; Hollinger, Khatami, Gugger, Hess, & Bassetti, 2006; Malow, Levy, Maturen, & Bowes, 2000).

2 Noise

Noise[3] is defined as unwanted sound and can have various adverse effects on humans[4] (see for comprehensive reviews Basner, Babisch, et al., 2013; Basner & McGuire, 2018; Münzel, Gori, Babisch, & Basner, 2014; Muzet, 2007). It is evident from this definition that noise cannot be evaluated in the absence of a recipient who "decides" if sound is perceived as noise: that is why, noise is rather considered as a psychological than a physical term. Nevertheless, certain physical sound characteristics (noise indicators) are usually related to noise effects and employed for dose-response relationships used for legislative purposes and noise regulation, as for example in the Night Noise Guidelines for Europe from the World Health Organization (WHO) or in national laws like the Swiss Noise Abatement Ordinance ("Lärmschutzverordnung"). Typical noise metrics are described in the following and illustrated in Figure 1.5 for two transportation noise events.

- Sound pressure level (SPL): defined as effective pressure in relation to a reference value. This reference depends on the medium, where the sound wave propagates and 20 µPa is usually used for propagation in air (Hellbrück & Ellermeier, 2004). In noise effects research, usually the maximum SPL of single events is used: a peak estimate, a physical quantity to approximate the sound strength as opposed to psychoacoustic measures, such as sound volume or perceived loudness. Its unit is decibel (dB) and dB(A) denotes the A-weighted SPL, an adjustment of the SPL for the range of human hearing. It is a logarithmic and not a linear scale: per 10 dB(A) increase, a doubling of the subjective sound volume is perceived (Federal Office for the Environment, 2009).
- Equivalent continuous SPL: time-averaged noise levels. For example, $L_{Aeq,24h}$ denotes the sound energy over a period of 24 h. But, the wider the time window, the bigger might be the difference between the averaged level and the perceived noise. Typical continuous noise indicators applied in noise regulation laws are: L_{den} as EU standard: sound energy over a period of 24 h with different weights for day, evening and night hours. Typically, a penalty factor of 5 dB is used for the evening hours, which needs to be defined by national laws (in Switzerland: 19:00-23:00), and a penalty factor of 10 dB for the nighttime (23:00-07:00); $L_{eq,Night}$: sound exposure during the nighttime hours (23:00-07:00); $L_{eq,Day}$: sound exposure during the daytime hours (07:00-23:00).
- Sound exposure level (SEL): this metric is like the equivalent continuous SPL, but adopts a reference period of 1 s.

[3] Interestingly, the German word "Lärm"–derived from the Italian "all' arme" which translates to "zu den Waffen!"–implicates the signalling effect of noise to warn animals and humans towards strong mechanical movements in the surrounding environment (see also Voss, 2001). The sound intensity, for example, provides information about the distance to the sound source. The English word "noise" on the other hand, can be related to the Latin word "nausia" and rather alludes to the effects of noise such as nausea or disgust.

[4] Of course, noise also affects wildlife (see Fahrig & Rytwinski, 2009): for example, species richness of birds was reduced in areas with high levels of anthropogenic noise when compared to quieter areas (Francis, Ortega, & Cruz, 2009). Birds are especially affected as their vocalizations, which directly impact reproduction success, might be masked by low-frequency transportation noise (Barber, Crooks, & Fristrup, 2010); for example, blackbirds populating the city used higher-frequency singing elements than blackbirds living in forests (Nemeth et al., 2013).

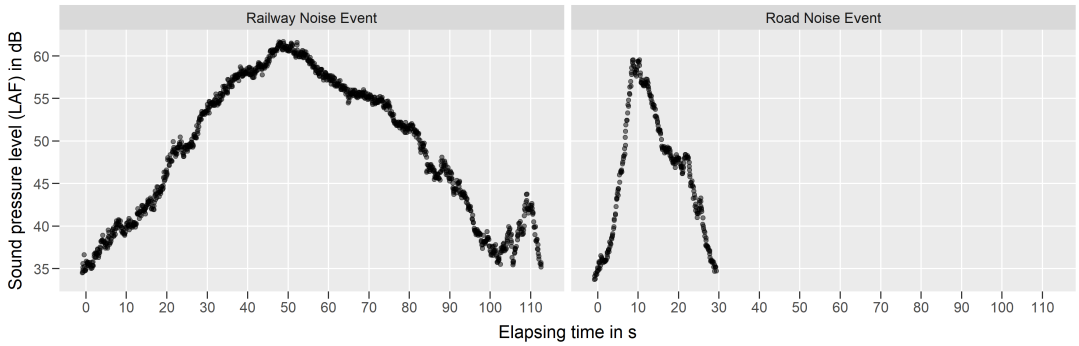

Figure 1.5: Sound pressure level (SPL) time courses for two different transportation noise events. The railway noise event (left side) and the road noise event (right side) are examples of the used acoustical stimuli in our experimental setup. The two events differ with respect to event duration, maximum SPL, and maximum slope of rise of the SPL. Railway noise event: duration: 112.6 s; maximum SPL: 61.7 dB(A); maximum slope of the SPL: 3.1 dB(A)/s. Road noise event: duration: 22.1 s; maximum SPL: 59.5 dB(A); maximum slope of the SPL: 5.0 dB(A)/s.

- Duration of an event.
- Slope of rise of the SPL (slopeSPL) as a description of the temporal characteristics of the SPL. Several methods were proposed to calculate this metric: a) slope to maximum: time to rise from a predefined difference in dB, 10 or 20, below the maximum SPL to the maximum SPL (Brink, Lercher, Eisenmann, & Schierz, 2008) or b) absolute maximum slope: maximum slope of several regression lines fitted to 15-dB spreads of the SPL (Rudzik et al., 2018).

The discussion about the most appropriate noise indicator to capture noise effects on health is central in the noise field (WHO, 2009). More specifically, noise metrics of single events might be more relevant to describe noise effects on sleep than all-night equivalent continuous levels, which necessarily entail information loss due to integration (WHO, 2011). In addition, the same $L_{Aeq,1h}$ can describe very different sound exposure situations: more continuous sound exposure situations with only small differences between maximum and average SPL or more intermittent sound exposure situations with long periods of low exposure and brief, distinct events of varying maximum SPL. Figure 1.6 depicts the two described prototypical noise exposure situations.

In general, transportation noise includes noise emitted from road, railway, and air traffic. Road traffic noise is composed of vehicle engine noise and rolling noise. Rolling noise originates from the contact between the road surface and the vehicle and depends on the quality and type of the tyres of the vehicle (i. e., the profile and the section width), the quality and surface of the road (i. e., roughness or elasticity), or the weather conditions (e. g., road traffic on a wet street produces more noise than a dry street) (Science for Environment Policy, 2017). Rolling noise typically dominates the noise emission for vehicle speeds higher than 40-50 km/h for light vehicles, such as passenger cars, or 80 km/h for heavy vehicles, such as trucks (Muzet, 2007).

Railway noise, on the other hand, mainly depends on:

- the speed of the train: depending on the speed, noise emissions primarily consist of rolling noise, aerodynamic noise, and auxiliary noise, such as fraction noise;
- the type of the train: passenger trains, high-speed or local trains, or freight trains;
- the quality of the track and the wheels, particularly regarding roughness (Muzet, 2007; Science for Environment Policy, 2017).

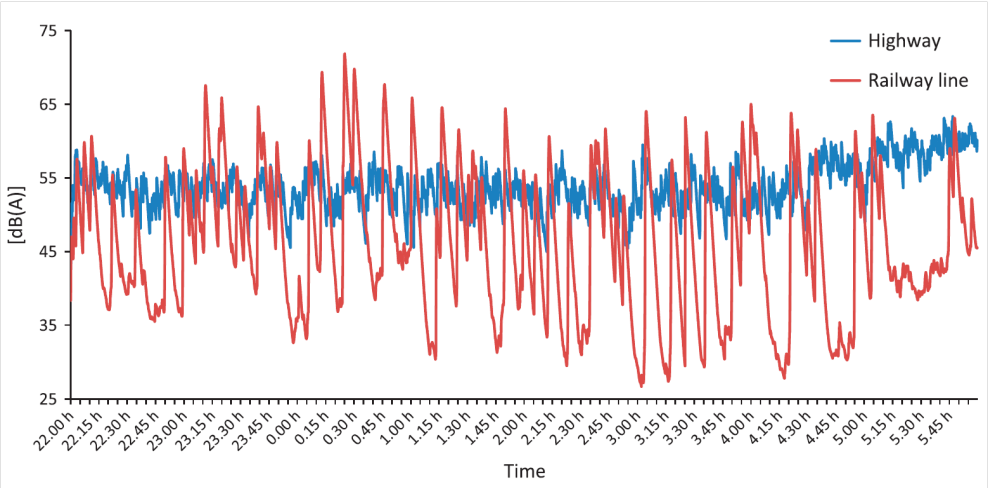

Figure 1.6: Sound pressure level (SPL) time courses over a period of 8 h for two different noise exposure situations. Both exposure scenarios had a normalized L_{Aeq} of 55 dB. The blue SPL time-course was recorded along a highway and depicts a continuous noise exposure situation. The red SPL time-course was recorded along a railway line and depicts a typical intermittent noise exposure situation. Reproduced from Wunderli et al. (2015, p. 2).

Applying the precautionary WHO threshold for the effect of nighttime noise on people (i. e., outdoor levels of 45 dB(A)), the following number of people in Switzerland are exposed to problematic SPL of the different sources during the nighttime: approximately 2.8 million people are exposed to road traffic noise, 330.000 people are exposed to railway noise, and approximately 95.000 are exposed to aircraft noise, of which the majority is living close to the major international airports (Federal Office for the Environment, 2009). In Switzerland, as in other European countries, road traffic noise is the most prevalent noise source during day- and nighttime, while railway noise is especially dominant during the nighttime (Federal Office for the Environment, 2009; Hanninen et al., 2014). Road noise emissions are expected to further increase in the coming years, particularly in urban areas (Federal Office for the Environment, 2009). For example, the number of people living south of Zurich Airport that are exposed to road traffic noise above $L_{Aeq,1h}$ 55 dB during day- and nighttime increased between 2001 and 2011 (Karipidis et al., 2014). It needs to be noted that these values typically refer to outdoor exposure levels, modelled at most exposed façade points of individual dwellings, and that indoor exposure levels are usually much lower. Outdoor-indoor differences depend on the window position and following median values can be used to approximate indoor exposure levels: 10.0-13.5 dB(A)

for open, 16.0-18.4 dB(A) for tilted, and 28.0-28.4 dB(A) for closed window situations (Basner et al., 2004; Locher et al., 2018).

2.1 Noise effects

Noise is considered a psychological stressor that is processed via direct (physiologic) and indirect (psychological) pathways (Babisch, 2002; Münzel et al., 2014; Recio, Linares, Banegas, & Diaz, 2016). Stress is ubiquitous and it is essential for survival that organisms can adapt to stressors (Karatsoreos & McEwen, 2011). When faced with a predator, for example, the increase of the sympathetic nervous tone is an adaptive physiological response leading to stress hormone secretion (e. g., cortisol, adrenaline, and noradrenaline) and increases in heart or respiration rates via the sympatho-adrenal-medular (SAM) axis preparing for "fight-or-flight" responses. The second stress pathway is activated to sustain the stress response with the release of cortisol via the hypothalamic-pituitary-adrenocortical (HPA) axis. When these stress systems are dysregulated or do not recover compared to their normal functioning, allostatic load or overload result as the price of adaptation, "the cumulative 'wear and tear' seen on body systems after prolonged or poorly regulated allostatic responses" (McEwen, 1998, p. 576). Typical variables to quantify allostatic load are systolic and diastolic blood pressure, waist-hip ratio, cholesterol levels, glycated haemoglobin (HbA_{1c}), or 12-h urinary cortisol levels (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997) while type-2 diabetes or cardiovascular disease (CVD) are seen as indicative for allostatic overload (Karatsoreos & McEwen, 2011).

Noise exposure during the nighttime is considered more adverse than during daytime for relevant health outcomes (Héritier et al., 2018; Jarup et al., 2008). Consequently, the disruption of sleep is the main hypothesized pathway for long-term exposure effects in addition to systemic stress system dysbalances (Münzel et al., 2017). Disruption of sleep might occur in response to stress or single stressors and can, in turn, act as a stressor per se (Palagini, Biber, & Riemann, 2014) impeding restorative processes during physiological sleep (Balkin, Rupp, Picchioni, & Wesensten, 2008; Conklin, Yao, & Richardson, 2018; Schmid et al., 2015). Accordingly, noise effects can be classified as acute (primary and secondary) or chronic (tertiary effects). Immediate noise effects on the organism are considered as primary effects and mainly include activation reactions during sleep (see Figure 1.7). Secondary effects describe the after-effects of a noise disturbed night sleep, such as reduced subjective sleep quality (Marks & Griefahn, 2005, 2007; Öhrström, 1995; Öhrström & Rylander, 1990), daytime sleepiness (Basner, 2008), or cognitive performance and mood decrements (Elmenhorst et al., 2010; Marks & Griefahn, 2005; Öhrström, 1995; Öhrström & Rylander, 1990; Schapkin, Falkenstein, Marks, & Griefahn, 2006). Tertiary effects are long-term effects, such as prevalence of certain adverse health outcomes, even though there is no agreement in the literature on defining long-term and whether it includes time intervals of a month, a year, or several years. Long-term noise exposure was demonstrated to affect blood pressure (Haralabidis et al., 2008) or stress hormone levels (Lefèvre et al., 2017) with possible negative repercussions on inflammatory pathways, the immune system, or

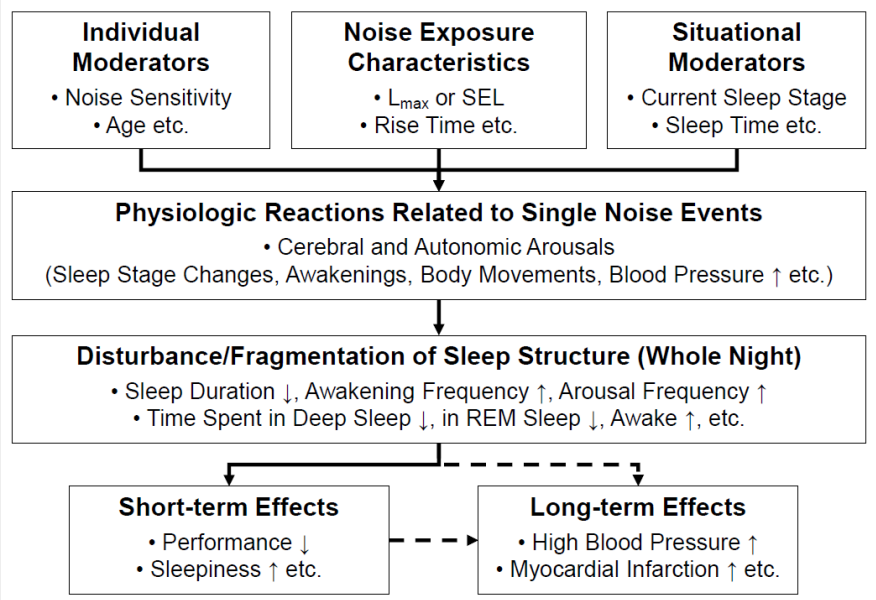

Figure 1.7: The reaction of the sleeper to single noise events, as measured using different arousal response markers, is modified by individual (e. g., age), acoustical (e. g., maximum SPL), and situational (e. g., sleep stage, time of night) factors. Recurrent sleep fragmentation affects the all-night sleep architecture (e. g., decreasing time spent in SWS or REM sleep), which has a negative impact on subsequent daytime performance or subjective sleepiness, and in turn, may lead to long-term effects, such as high blood pressure, when individuals are exposed to nighttime noise over longer periods of time (dashed lines). Adapted from Basner and McGuire (2018, p. 3).

endothelial functioning (Schmidt et al., 2013, 2015) and increase the risk for cardiovascular, respiratory, or metabolic pathologies (Münzel et al., 2014; Recio et al., 2016).

Noise sensitivity

Noise sensitivity is considered a trait-like evaluative and perceptive predisposition towards environmental noise in general (Schütte, Marks, Wenning, & Griefahn, 2007), which influences the subjective evaluation of sleep (Marks & Griefahn, 2007) or nighttime noise annoyance (Miedema & Vos, 2003; Shepherd, Welch, Dirks, & Mathews, 2010). Noise sensitive individuals might have higher attentive and discriminative abilities towards noise, might evaluate noise as more negative and, in turn, demonstrate enhanced emotional reactivity than noise resistant individuals resulting in higher negative affect (Stansfeld, 1992). It is possible that noise sensitivity is the result of a specific configuration of the underlying neural network (i. e., neurotransmitter availability, or even morphometry such as grey matter volume or cortical thickness), but the biomarker of noise sensitivity has not yet been identified. However, basic auditory information processing differed between noise sensitive and resistant individuals: noise sensitive individuals had reduced sensory gating, i. e. the ability to block information processing of irrelevant sensory information, which was demonstrated using the amplitude of the P50 during an auditory discrimination task (Shepherd, Hautus, Lee, & Mulgrew, 2016). In addition, noise sensitive individuals had a reduced ability for sound feature discrimination as assessed by means

of mismatch negativity (Kliuchko, Heinonen-Guzejev, Vuust, Tervaniemi, & Brattico, 2016). And, noise sensitive individuals had higher HR increases in response to single transportation noise events during wakefulness than noise resistant individuals (Di Nisi, Muzet, Ehrhart, & Libert, 1990; Griefahn & Di Nisi, 1992). However, this was not reported univocally (Öhrström, Bjorkman, & Rylander, 1988). On the other hand, it is not well understood whether sleep- and wake-related noise sensitivity share a physiological basis or represent different concepts (Shepherd et al., 2016). The observed difference in HR in response to single transportation noise events between noise sensitive and resistant individuals during wakefulness was not present when the same individuals were tested during sleep (Di Nisi et al., 1990). In addition, the average HR increase observed during sleep was approximately 10 % higher than during wakefulness despite lower SPLs (− 15 dB) used during the night (Di Nisi et al., 1990). This exaggerated autonomic response during sleep might comply with an evolutionary reasoning as preparing the organism for a potential behavioural response to stimuli during sleep that imply threat or danger.

2.2 Effects of nighttime transportation noise on sleep

A multitude of reviews is concerned with the effects of nighttime transportation noise on sleep (Basner, Babisch, et al., 2013; Basner et al., 2017; Basner & McGuire, 2018; Griefahn & Muzet, 1978; Hume, Brink, & Basner, 2012; Muzet, 2007; Pearsons, Barber, Tabachnick, & Fidell, 1995; Pirrera, De Valck, & Cluydts, 2010; WHO, 2009). However, the focus was more on reporting all noise effects on sleep rather than exploring whether results were consistent between experiments, noise conditions, or age groups. Consequently, in the following, laboratory and ambulatory experiments using PSG and different noise exposure situations (i. e., continuous and intermittent) were briefly summarized with respect to consistency of results for sleep macrostructure (e. g., amounts spent in different sleep stages, TST, sleep, SE, or onset latencies to different sleep stages) and microstructure (arousal response markers, such as awakenings or CA). Differences between transportation noise sources (i. e. railway, aircraft, road noise) were neglected for this purpose as effects were not systematic; the controversial results might be explained by differences in sound composition of individual noise events, such as spectral or temporal properties (Basner et al., 2011).

Sleep macrostructure

Particularly amounts of REM sleep and SWS have been reported to be affected by nighttime noise exposure though not univocally. For all results, noise effects have been compared to a quiet night, respectively. All acoustical measures refer to indoor exposure levels, usually measured at the ear of the sleeper. Typically, pre-recorded noise exposure situations were used and played back to individuals sleeping in the laboratory.

REM sleep. A reduction in time spent in REM sleep as well as an increase in REM sleep latency were demonstrated for continuous road traffic at L_{Aeq} 40-45 dB (Eberhardt, Ståle, & Berlin, 1987; Griefahn, 1986), but also for intermittent noise exposure, especially for railway noise at L_{Aeq} 50 dB (Griefahn, Marks, & Robens, 2006). Similarly, REM sleep was suppressed

in young male adults, exposed to high-intensity intermittent and continuous white noise with 93 dB(A) and 90 phon, respectively (Okuma & Honda, 1978; Scott, 1972). Others showed a dose-response relationship with REM sleep more reduced for L_{Aeq} 75 dB than for 45 dB (Terzano, Parrino, Fioriti, Orofiamma, & Depoortere, 1990). The majority, however, did not report any changes in amount or latency of REM sleep for young male individuals exposed to high-intensity tone pulses (90-100 dB(A) in 40-, 10-, 2.5-, or 1-s intervals) (Nakagawa, 1987) or for young and middle-aged individuals exposed to intermittent transportation noise (Basner et al., 2011; Basner & Samel, 2005; Libert et al., 1991; Saremi et al., 2008; Smith et al., 2017).

SWS. A reduction in time spent in SWS was demonstrated for intermittent noise exposure, similarly, for road, railway and air traffic noise (Basner et al., 2011; Basner & Samel, 2005; Eberhardt et al., 1987; Griefahn et al., 2006; Thiessen, 1978) and continuous white noise exposure with a dose-response relationship (Terzano et al., 1990). Others, however, did not report changes in SWS for high-intensity continuous and intermittent white noise exposure (Nakagawa, 1987; Okuma & Honda, 1978; Scott, 1972) or transportation noise exposure (Libert et al., 1991; Saremi et al., 2008; Smith et al., 2017). An increase, on the other hand, of "deep sleep" was reported for young individuals exposed to continuous road traffic noise (L_{Aeq} 47 or 60 dB; + 2.5 % or + 4.6 %) (Thiessen & Lapointe, 1983). But, deep sleep was defined upon spindle presence: as a result, the effect is nearly incomparable with the above reported results as, spindles are, for example, absent during N1 sleep, REM sleep, and even parts of N2 sleep or SWS.

Additionally, experiments were conducted in the participant's home using ambulatory PSG and residential noise in their bedrooms as noise exposure. As a result, per design, there have been no quiet nights for comparisons. However, differences in noise exposure between nights or individuals, effects of sound insulation interventions or characteristic changes in noise exposure, such as opening of an additional landing strip, were used to evaluate noise effects. Some reported no differences in sleep structure between low and high exposure nights within individuals (Basner et al., 2004) while others reported a shorter REM sleep duration ($-$ 31.8 min) for individuals habitually exposed to railway noise with single events above a maximum indoor SPL of 50 dB(A) as compared to individuals exposed to below 50 dB(A) noise events (Aasvang, Overland, Ursin, & Moum, 2011). Changing the sleeping room to a more quiet façade, increased the amount of REM sleep ($+$ 14.0 min) and decreased REM sleep latency ($-$ 15.0 min) in young and middle-aged individuals habitually exposed to heavy road traffic noise[5] (Vallet, Gagneux, Blanchet, Favre, & Labiale, 1983). Reducing the nighttime noise exposure using sound insulation of bedroom windows resulted in an increase in combined N2 and SWS ($+$ 5.0 min) in young male individuals habitually exposed to heavy road traffic noise[6] (Eberhardt & Akselsson, 1987) or an increase in SWS ($+$ 5.5 min, sleep stage four, scored according to rules of Rechtschaffen and Kales (1968)) in young and older individuals

[5]Habitual indoor L_{Aeq} was between 39-51 dB and noise intervention reduced the L_{Aeq} between 2 and 14 dB; all measurements were taken inside the bedroom.

[6]Mean habitual indoor L_{Aeq} was 36 dB and noise intervention reduced L_{Aeq} by 8 dB on average; all measurements were taken inside the bedroom.

habitually exposed to heavy road traffic noise[7] (Wilkinson & Campbell, 1984). As compared to laboratory experiments where virtually all experiments employed a pre-specified bedtime regimen (usually between 23:00 and 07:00 for Basner et al., 2011; Griefahn et al., 2006; Saremi et al., 2008; Smith et al., 2017), individuals in the field are allowed to follow their habitual daily routine and can adhere to habitual bedtimes. This experimental setup, however, complicates the interpretation of sleep durations. For example, none of the cited field experiments reported exact bed times and it remains unknown whether the individual sound insulation interventions impacted on the individual decision when to lie down, go to sleep, and rise the next morning (i. e., time in bed): as a result, it is possible that modifications of REM sleep, which is under strong circadian control, were only due to a delay or advance of the sleep episode under noise insulation conditions as compared to the habitual noise exposure situation. And, it is of note that the increased amount of time spent in sleep stage 4 for the sound insulation intervention reported by Wilkinson and Campbell (1984) was accompanied by an increase in TST, though, not significant. Whether this was the result of a prolonged time in bed or an increase in SE (i. e., TST per time in bed) was, however, not reported.

Consequently, we can safely conclude, that the field is far from a consensus regarding the effects of noise on amounts of REM sleep or SWS. In addition, the hypothesis that REM sleep might be more disturbed by continuous and SWS more by intermittent noise needs further evaluation (Eberhardt et al., 1987; Pirrera et al., 2010).

Sleep microstructure

The most consistent result for noise effects on sleep is that nighttime noise exposure disrupts sleep continuity as demonstrated for different arousal response markers: during noise exposure, all-night number of CA (Basner et al., 2011; Saremi et al., 2008), sleep stage changes (Basner, Glatz, Griefahn, Penzel, & Samel, 2008; Basner et al., 2011), and awakenings (Basner, Glatz, et al., 2008; Basner & Samel, 2005; Thiessen & Lapointe, 1983) increased and individuals spent more time awake (Griefahn et al., 2006; Vallet et al., 1983) as compared to noise-free or more quiet conditions. Similarly, under high-intensity tone pulse exposure, individuals spent more time awake, had more awakening reactions and sleep stage changes (Nakagawa, 1987; Scott, 1972; Terzano et al., 1990)–effects that demonstrated clear exposure intensity-response relationships with the all-night L_{Aeq} (Terzano et al., 1990) or with the inter-stimulus intervals (Nakagawa, 1987). In conclusion, even though there is general agreement about the sleep disrupting effect of noise there is no consensus which arousal response marker is affected.

For intermittent noise with well-defined events, which have a clear on- and offset, it can be tested whether arousal responses occur in temporal proximity to single noise events. Most authors used a fixed time window around a single event, typically a multiple of the length of a single 30-s scoring window, e. g. 30, 60, or 90 seconds (Basner et al., 2011; Griefahn, Brode, et al., 2008; Marks, Griefahn, & Basner, 2008; Smith et al., 2017): an arousal response, occurring during this time window is considered an event-related activation. Event-related

[7] Habitual indoor L_{Aeq} was between 42-52 dB and noise intervention reduced L_{Aeq} by 5.8 dB on average; all measurements were taken inside the bedroom.

activation probabilities are then calculated as ratios between the number of event-related arousal responses and the number of single noise events. But, an arousal response might not be truly event-related and could have occurred spontaneously at the same time. Consequently, there is consensus in the literature to adjust event-related activation probabilities using spontaneous activation probabilities (Basner et al., 2011; Brink et al., 2009; Griefahn, Brode, et al., 2008; McGuire, Müller, Elmenhorst, & Basner, 2016; Smith et al., 2017). Spontaneous activation probabilities are calculated using "virtual" events, i. e., periods during noise-free nights with the same duration and distribution across the night as during eventful noise nights. Probability of awakening and CA were significantly higher during actual compared to virtual noise events (Basner, Glatz, et al., 2008; Basner et al., 2011; Eberhardt et al., 1987; Saremi et al., 2008; Smith et al., 2017; Vernet, 1979). Furthermore, activation probabilities were significantly related to acoustical (i. e., increase with maximum SPL, slope of rise of single events, the number of noise events per night), personal (i. e., increase with age) and situational parameters (i. e., sleep stage during noise onset, N1 with a higher and SWS with a lower probability when compared to N2 sleep, time of night) (Basner et al., 2011; Elmenhorst et al., 2012; Marks et al., 2008). Results were inconclusive regarding activation probability from REM sleep: an increase (Elmenhorst et al., 2012), a decrease compared to N2 sleep (Basner et al., 2011), and a non-significant difference between the two sleep stages (Marks et al., 2008) were reported. Regarding age, CA and awakening probabilities increased (Basner et al., 2011; Elmenhorst et al., 2012), while others did not report any differences in event-related activation probabilities (Saremi et al., 2008). A careful read of the Saremi et al. paper, on the other hand, raises the question about the unusual low number of all-night CA (19.0-37.3 vs. 83.0-128.0 reported as norm values for the included age group) and the unusual high percentage of SWS when compared to normative data or others data sets (Azarbarzin et al., 2015; Bonnet & Arand, 2007; Sforza et al., 2008).

It can be concluded that transportation noise effects on sleep macrostructure are rather subtle, not very consistent between experiments, and if present, difficult to explain as bedtime regimen differed between studies and settings: in most field studies, time in bed was neither controlled nor reported and virtually all laboratory experiments restricted bedtimes to a fixed schedule instead of allowing individuals to adhere to individual bedtimes (usually between 23:00 and 07:00 h for most laboratory esperiments as Basner et al., 2011; Griefahn et al., 2006; Saremi et al., 2008; Smith et al., 2017). Rather than affecting sleep macrostructure, there is more consensus between studies regarding the sleep disruptive effects of noise, even though it is not clear which arousal response marker is most affected (awakenings, CA, or AA). Furthermore, the observed all-night increase in CA of an additional 1.7 CA per h TST during noise exposure as compared to noise-free nights (Basner et al., 2011) can be considered as mild when compared to the CA increase seen in sleep-related disorders of an additional 53 CA per h TST in OSAS patients as compared to age-matched healthy controls (Parrino et al., 2005).

2.3 Vulnerable times

From a theoretical point of view, two time points during sleep should be especially vulnerable to noise effects (see also Griefahn, Marks, & Robens, 2008; Muzet, 2007): the sleep onset period and the early morning hours when auditory responsiveness is increased due to homeostatic sleep pressure dissipation and the increased circadian wake promotion (Akerstedt et al., 2002; Merica & Gaillard, 1986).

Contrary to the strong theoretical hypothesis, EEG-verified sleep onset latency[8] was largely unaffected by transportation noise exposure (Basner et al., 2011; Eberhardt et al., 1987; Saremi et al., 2008; Thiessen & Lapointe, 1983) or high-intensity white noise stimulation (Okuma & Honda, 1978; Scott, 1972; Terzano et al., 1990), though not for all (Nakagawa, 1987). On the other hand, intermittent transportation noise exposure, was shown to selectively increase SWS latency (Basner et al., 2011; Griefahn et al., 2006; Saremi et al., 2008). While continuous, more predictable noise might be cancelled out from the brain during the sleep onset process, single noise events may arouse the sleeper and result in a disturbed sleep deepening process during the sleep onset phase. Nevertheless, some habituation/adaptation might occur: highly predictable tone pulses, applied every 22 seconds during day- and nighttime over a period of 30 days, did not result in an increased sleep latency though subjective sleep latency increased with stimulus intensity (Townsend, Johnson, & Muzet, 1973). It is more likely to be awakened or aroused by a noise event in the early morning hours (Basner et al., 2011; Basner & Siebert, 2006; Marks et al., 2008), but falling back to sleep might also be more difficult under conditions of reduced sleep pressure in the early morning hours than during the sleep onset period (Basner et al., 2004). Results differ when reactions were not assessed using EEG but actimetry in the field: noise-related reactions did not increase across the night (Brink et al., 2008; Horne, Pankhurst, Reyner, Hume, & Diamond, 1994). However, EEG-verified awakenings are not the same as actimetry-verified motility reactions as the latter can also occur during wakefulness whereas the former occurs per definition from sleep.

[8] Several definitions for the sleep onset latency exist. It is defined as the time between lights off and the onset of the respective sleep stage; for example, sleep latency to SWS is the time to onset of SWS. Latency to SWS is preferred over latency to N2 sleep as the onset of deep sleep is usually considered a more stable period than N2 sleep.

Chapter 2

Objectives & Methods of the thesis

The main objective of the current thesis was to characterize the effects of nighttime transportation noise and age on sleep microstructure. Sleep is not a stable, but a dynamic process and sleep macrostructure as the quantification of sleep stages is build up by distinct transient events, such as sleep spindles, SO, or arousal responses (Halasz & Bodizs, 2013). Results on nighttime transportation noise effects on sleep macrostructure were not univocal or consistent; there is more consensus that nighttime noise affects sleep microstructure, even though it is not clear which arousal response marker is most affected (awakenings, CA, or AA) (Basner, Glatz, et al., 2008; Basner et al., 2011; Griefahn, Brode, et al., 2008). Methodologically, effects on sleep microstructure can be investigated on the all-night level comparing rates or number of arousal responses between noise exposure and noise-free nights as well as on the level of a single noise event comparing activation probabilities between actual and "virtual" noise events. While age affects both sleep macro- and microstructure, age-related changes are especially evident in the sleep microstructure as indexed by an increase in sleep fragmentation and a marked decline in sleep spindles (Carrier et al., 2001; Landolt et al., 1996; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Purcell et al., 2017; Schwarz et al., 2017; Warby et al., 2014). Because of the age-related alterations in sleep macro- and microstructure as well as the higher self-reported noise sensitivity in older than in young individuals (Matsumura & Rylander, 1991; Schreckenberg, Meis, Kahl, Peschel, & Eikmann, 2010), older individuals are generally considered at risk for nighttime noise effects on sleep (Basner & McGuire, 2018; Muzet, 2007). However, the existing empirical data basis of noise effects on sleep is still very limited to draw reliable conclusions about potential vulnerable groups, such as the older population.

1 Methods

All data used for this thesis were acquired in a sample of healthy young ($N = 26$, 19-33 years, 12 women) and older individuals ($N = 18$, 52-70 years, 9 women) that underwent a polysomnographic (PSG) six-day laboratory study. They had two noise-free (always the first and the last night; $L_{Aeq,1h}$ of 30 dB at the ear of the sleeper) and four noise nights (four different noise exposure situations with two more continuous and two more eventful noise scenarios; $L_{Aeq,1h}$ of 45 dB at the ear of the sleeper; see Figure 1.6 in the Introduction for an illustration of the different noise exposure situations), which either contained road noise (three nights) or railway noise (one night). Participants in the young group were balanced according to the two homozygous variants of a polymorphism in the clock gene PER3 (Dijk & Archer, 2010; Viola et al., 2007)

and sex. The older group was only balanced according to sex, although information about the PER3 genotype was collected. During the nights, PSG, continuous systolic and diastolic blood pressures–approximated by the pulse transit time–, and body movements (using a sensor unit, which was placed under the bed mattress) were recorded. During scheduled wakefulness, participants underwent cognitive performance testing on different domains (memory, working memory, and sustained attention) at regular intervals four times (2.5, 6.5, 10, 13 hours after scheduled wake-up time). Subjective sleepiness and well-being were sampled every 30 minutes during the first 3 hours after wake-up time and the last 4.5 hours before bed time as well as every 2 hours in between. Subjective sleep quality was assessed every morning. For more detailed information on study procedures, applied stimuli and tests, it is referred to the individual chapter (for a schematic overview of the experimental protocol see Chapter 3, Figure 3.1).

To be complete, other variables, mainly concerning the stress axis and the carbohydrate metabolism, were examined, which are not part of this thesis but were evaluated elsewhere (Thiesse et al., 2019, 2018). That included salivary cortisol and melatonin levels, assessed twenty times during the day at the same time points as the assessment of well-being. During the night, the urine was collected to assess all-night catecholamine levels, i. e. creatinine, normalized epinephrine and norepinephrine. 120-minutes 75-gr oral glucose tolerance tests were performed on the mornings of days 1, 5, and 6 to evaluate fasting glucose and insulin as well as glucose tolerance and insulin sensitivity. In addition, serum inflammatory markers (i. e., Interleukin 6, tumor necrosis factor alpha, and C-reactive protein) as well as adipokines (adiponectin and leptin) were assessed upon fasting during the mornings of days 1, 5, and 6.

2 Aims

The aim of the first paper (Chapter 3) was to evaluate the role of sleep spindles, spontaneous NREM sleep-related brain oscillations, for protecting sleep in the presence of transportation noise exposure. It was demonstrated that young individuals with higher all-night sleep spindle rates had higher CA thresholds for a variety of common hospital-recorded noise events than individuals with lower all-night sleep spindle rates (Dang-Vu et al., 2010). Based on this finding, we included not only young but older individuals to test whether older–with lower all-night spindle rates due to physiological aging–are more sensitive to transportation noise exposure during sleep than young individuals (as indexed by number of awakenings, CA, sleep stage changes, or percentage N1 sleep). Furthermore, we applied not only eventful but more continuous noise to mimic ecological valid noise exposure situations and tested differences between the different exposure situations.

In the second paper (Chapter 4), we analyzed the microstructural architecture of NREM sleep using EEG arousals as a marker for transient activations. The aim was threefold. As EEG arousals are not distributed randomly across the night (Halasz et al., 2004; Terzano & Parrino, 2000; Terzano et al., 2000), we examined the temporal variation of EEG arousals on the level of the sleep cycle (within-cycle effect) and over the course of the night (across-cycle effect). The all-night number of EEG arousal undergo a marked increase with aging (Bonnet & Arand,

2007; Boselli et al., 1998; Terzano et al., 2002), so that we aimed to test whether within- and across-cycle effects vary with aging. Third, building on the notion that transportation noise exposure increases the number of all-night EEG arousals (Basner et al., 2011; Saremi et al., 2008), we were interested whether EEG arousals during noise nights had a similar temporal distribution pattern than during undisturbed nights.

The aim of the third paper (Chapter 5) was twofold. As there is little systematic evaluation of the frequency of occurrence of the different arousal response markers in the literature, we compared arousal rates of different markers and further investigated modifications with age. Second, we evaluated the probability of occurrence with transportation noise exposure for each marker to evaluate its reactivity to auditory stimulation. As the autonomic nervous system might be an especially sensitive marker, we were primarily interested in the difference between AA and CA. We hypothesized that frequency of occurrence, both spontaneously as well as event-related, will be highest for AA, followed by CA, and then AWR–at least in the young. Additionally, we were interested how body movements during sleep relate to this arousal response hierarchy.

Chapter 3

Sleep spindle characteristics and arousability from nighttime transportation noise exposure in healthy young and older individuals

Authors

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Contributions

FR, LT, CG contributed to data collection; FR, LT, CC performed the analysis; FR wrote the manuscript; LT, RP, JMW, MB, MF, HH, ICE, CG, DV, NPH, MR, CC provided fruitful interpretation of the data; FR, LT, RP, JMW, MB, MF, DV, NPH, MR, CC designed the data acquisition protocol; RP created and analyzed the acoustical stimuli; all authors participated in the revision of the manuscript.

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ABSTRACT

Study Objectives

Nighttime transportation noise elicits awakenings, sleep-stage changes, and electroencephalographic (EEG) arousals. Here, we investigated the potential sleep-protective role of sleep spindles on noise-induced sleep alterations.

Methods

Twenty-six young (19-33 years, 12 women) and 18 older (52-70 years, 9 women) healthy volunteers underwent a repeated measures polysomnographic six-day laboratory study. Participants spent one noise-free baseline night, followed by four transportation noise exposure nights (road traffic or railway noise; continuous or intermittent: average sound levels of 45 dB, maximum sound levels of 50-62 dB), and one noise-free recovery night. Sleep stages were scored manually and fast sleep spindle characteristics were quantified automatically using an individual band-pass filtering approach.

Results

Nighttime exposure to transportation noise significantly increased sleep EEG arousal indices. Sleep structure and continuity were not differentially affected by noise exposure in individuals with a low versus a high spindle rate. Spindle rates showed an age-related decline along with more noise-induced sleep alterations. All-night spindle rates did not predict EEG arousal or awakening probability from single railway noise events. Spindle characteristics were affected in noise exposure nights compared to noise-free nights: we observed a reduction of the spindle amplitude in both age groups and of the spindle rate in the older group.

Conclusions

We have evidence that spindle rate is more likely to represent a trait phenomenon, which does not seem to play a sleep-protective role in nighttime transportation noise-induced sleep disruptions. However, the marked reduction in spindle amplitude is most likely a sensitive index for noise-induced sleep alterations.

1 Introduction

Why are some individuals' brains more effective in canceling out noise during sleep than others? Sleep-related noise sensitivity exhibits marked inter-individual variability (McGuire et al., 2016): some are difficult to arouse, while others are repeatedly disturbed by external stimuli such as nighttime transportation noise that elicits additional awakenings, sleep stage changes, or electroencephalographic (EEG) arousals (Basner et al., 2011; Griefahn, Brode, et al., 2008; Marks et al., 2008; Muzet, 2007). EEG arousals are defined as abrupt shifts in EEG frequency towards higher frequencies (Bonnet et al., 1992) and differ from awakenings in their transitory nature and concomitant changes in heart rate dynamics (Griefahn, Brode, et al., 2008). Sleep spindles–sleep-related EEG oscillations, that occur spontaneously during non-rapid eye movement (NREM) sleep–showed a sleep-protective function (Dang-Vu et al., 2010). Spindles are identified by their frequency (approx. 12-15 Hz for fast spindles), duration (typically between 0.5-2 s (Purcell et al., 2017; Warby et al., 2014), and characteristic shape from cortical EEG recordings and their density has high inter-individual variation (Purcell et al., 2017). Individuals with higher all-night sleep spindle rates had higher EEG arousal thresholds for a variety of commonly experienced noise types presented during NREM sleep than individuals with lower all-night sleep spindle rates (Dang-Vu et al., 2010).

Neurons in the thalamic reticular nucleus (TRN) play a pacemaking role for spindle oscillations, but the spindle event itself is network-generated within a corticothalamocortical circuitry (Steriade, 1999, 2006). TRN neurons potentiate thalamocortical (TC) projection cells whose rhythmic inhibitory post-synaptic potentials result in excitatory postsynaptic potentials in the cortex (Steriade, 1999). It has been hypothesized that TC cell firing during spindles gates afferent signaling to the cortex (Steriade, 2006) in order to isolate the cortex from environmental throughput and thus facilitate off-line memory consolidation or brain plasticity processes (Astori et al., 2013; Dang-Vu, 2012). Indeed, differential information processing of auditory stimuli–usually very brief, only several ms lasting stimuli–during spindle presence relative to absence was demonstrated in humans using event-related potential studies (Cote et al., 2000; Elton et al., 1997; Schabus et al., 2012) and combined event-related EEG/fMRI studies (Dang-Vu et al., 2011; Schabus et al., 2012). However, there is less consensus on the sleep-protective role of spindles in the presence of noise stimuli with higher ecologic validity (i. e., non-artificial and longer lasting noise stimuli).

Additionally, age plays an important role for noise-induced sleep disruptions: with aging the neural network exhibits marked transformations such as a deterioration in grey and white matter (Raz et al., 2010; Resnick et al., 2003; Thambisetty et al., 2010) that might impact on sleep structure and EEG oscillations (Mander, Winer, & Walker, 2017; Sprecher et al., 2016). A decrease in sleep efficiency and slow wave sleep (SWS) or an increase in the number of spontaneous EEG arousals are typical age-related changes in sleep macro- and microstructure (Boselli et al., 1998; Crowley, Trinder, & Colrain, 2002; Schwarz et al., 2017). Spindle characteristics also exhibit age-related alterations: when comparing to younger adults or adolescents, a reduction in spindle rate (Crowley et al., 2002; Knoblauch et al., 2005; Mander et al., 2014; Mander, Winer,

& Walker, 2017; N. Martin et al., 2013; Nicolas, Petit, Rompre, & Montplaisir, 2001; Purcell et al., 2017; Warby et al., 2014), duration (Crowley et al., 2002; Guazzelli et al., 1986; Knoblauch et al., 2005; N. Martin et al., 2013; Nicolas et al., 2001; Purcell et al., 2017), and amplitude (Guazzelli et al., 1986; Knoblauch et al., 2005; N. Martin et al., 2013; Purcell et al., 2017; Warby et al., 2014) are typically reported. Age comparisons for spindle frequency, however, indicate a small (Crowley et al., 2002; Nicolas et al., 2001) but a largely inconsistent (Knoblauch et al., 2005; N. Martin et al., 2013; Purcell et al., 2017; Warby et al., 2014) increase with aging. For example, reduced white matter integrity in the relevant spindle circuitry (i. e., corpus callosum or thalamic radiation) was associated with a reduced spindle rate in aging (Mander, Winer, & Walker, 2017). As a result of marked age-related sleep changes, noise sensitivity, a trait-like evaluative and perceptive predisposition towards environmental noise in general, might increase with aging (Schreckenberg et al., 2010; Van Gerven, Vos, Van Boxtel, Janssen, & Miedema, 2009), which in turn can influence the subjective evaluation of sleep (Marks & Griefahn, 2007) or nighttime noise annoyance (Miedema & Vos, 2003).

This polysomnographic (PSG) study explores the potential sleep-protective role of sleep spindles in healthy young and older adult volunteers exposed to nighttime transportation noise. As real-world nighttime noise from road traffic and railways may include both intermittent periods as well as rather continuous noise, the used noise scenarios reflected both continuous (two nights) and more eventful (two nights) noise exposure situations to ensure high ecologic validity. In a first step, all-night transportation noise effects on sleep outcome variables (i. e., sleep structure and continuity) and spindle characteristics (i. e., rate, duration, frequency, and amplitude) were evaluated. In a second step, all-night spindle rate was related to sleep outcome variables: if spindles have sleep-protective features, sleep structure and continuity in individuals with a high all-night spindle rate should be less affected by noise exposure than in individuals with a low all-night spindle rate; the same should apply for young individuals who have higher all-night spindle rates than older individuals. In a last step, we carried out an event-related analysis and included all-night spindle rate among other sleep-related and acoustical parameters (Basner et al., 2011; Griefahn, Brode, et al., 2008; Marks et al., 2008) with the aim to predict EEG arousal and awakening probability from single railway noise events. In addition, we evaluated spindle characteristics during exposure and non-exposure periods to test reactive spindle activity (Antony & Paller, 2017; Sato, Fukuoka, Minamitani, & Honda, 2007) and relations to acoustical characteristics of the railway noise events (Pivik, Joncas, & Busby, 1999).

2 Methods

2.1 Participants

Forty-four healthy volunteers of two age groups (26 young: 19-33 years, 12 women; 18 older: 52-70 years, 9 women) were selected for the study. All participants were free from any acute or chronic illness and current medication as assessed by means of clinical history, physical examination by a study physician, and routine blood and toxicological urine testing.

Table 3.1: Demographic data and questionnaire scores (M and SD) of the sample split by age

Sample characteristics	young	older	
N (f, m)	26 (12, 14)	16 (8, 8)	
Age (y)	24.58 (3.51)	60.83 (5.90)	*
BMI (kg/m^2)	22.21 (2.10)	22.02 (2.13)	
ESS	4.85 (2.84)	5.75 (2.96)	
PSQI	2.19 (1.10)	2.88 (1.63)	
PSQI Sleep Duration	7.88 (0.63)	7.81 (0.36)	
MCTQ Sleep Duration work	8.13 (0.87)	8.10 (0.87)	
MCTQ Sleep Duration free	8.40 (0.97)	8.29 (0.89)	
MCTQ MSF_{sc}	4.27 (0.67)	3.33 (1.11)	*
STAI-trait anxiety	26.64 (7.40)	28.31 (6.47)	
LEF-K	10.96 (4.04)	14.44 (3.56)	*
NoiSeQ Global	1.23 (0.43)	1.59 (0.34)	*
NoiSeQ Sleep	1.12 (0.64)	1.38 (0.52)	

Note. F refers to female; m: male; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; MCTQ: Munich Chronotype Questionnaire; MSF_{sc}: Mid sleep on free days corrected for sleep duration; STAI: State-Trait Anxiety Inventory; LEF-K: Lärmempfindlichkeitsfragebogen (German version); NoiSeQ Global: Noise Sensitivity Questionnaire-global score; NoiSeQ Sleep: Noise Sensitivity Questionnaire-subscale 'Sleep'; *: Significant difference between age groups ($p < 0.05$, Welch's two-sample t-test that is somewhat invariant to unequal sample sizes and variances).

All participants slept habitually 8 ± 1 h, showed good subjective sleep quality (Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), PSQI ≤ 5), normal general daytime sleepiness (Epworth Sleepiness Scale (Johns, 1991), ESS ≤ 10), and had no signs of sleep disorders, such as sleep-related movement and breathing disorders (confirmed via PSG during one screening/adaptation night prior to study admission). They were free from depressive symptoms (Beck Depression Inventory, BDI-II < 9) and had normal sex and age-appropriate hearing thresholds (maximum hearing loss of the better ear no greater than the 10th percentile of an otologically normal population (International Organization for Standardization, 2000) at the frequencies 250, 500, 1000, 2000, 3000 and 4000 Hz) tested manually with an audiometer (Bosch ST-10, Stuttgart, Germany). Further exclusion criteria comprised smoking, night shift work within three months or transmeridian travel within one month prior to study start, extreme circadian preference (Munich Chronotype Questionnaire (MCTQ) (Roenneberg, Wirz-Justice, & Merrow, 2003), MCTQ $MSF_{sc} < 2$ or MCTQ $MSF_{sc} \geq 7$), or drug misuse. Participants were not selected upon habitual noise exposure or sensitivity to noise but self-reported noise sensitivity varied considerably as measured by the short version of the German Lärmempfindlichkeitsfragebogen (LEF-K) (Zimmer & Ellermaier, 1998) and the Noise Sensitivity Questionnaire (NoiSeQ) (Schütte et al., 2007) (Table 3.1).

Two young participants did not finish the experiment (both quitted on the fifth day for personal reasons) and were substituted in order to maintain the balancing but data were nevertheless included for analysis. Two participants of the older group dropped out of the experiment due to medical reasons (one female: severe back pain that required pain medication; one male: general

discomfort and headaches). They were not substituted and their entire data were excluded. In total, data of 42 participants were considered for the analysis.

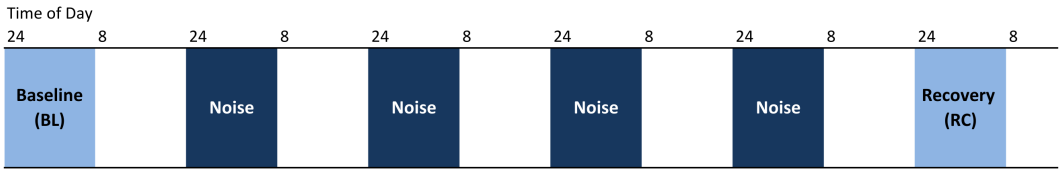
The study protocol, screening questionnaires, and consent forms were approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, Switzerland, #2014-121) and conformed to the tenets of the Declaration of Helsinki. All participants gave written informed consent prior to study participation and received financial compensation for participation. Data acquisition took place between October 2014 and June 2016.

2.2 Protocol and procedure

The protocol comprised six consecutive nights and days in the sleep laboratory under continuous PSG recording. Participants were exposed to different transportation noise scenarios during four nights and spent two noise-free nights (Figure 3.1). Noise-free nights were always the first (baseline night: BL) and the last night (recovery night: RC). The transportation noise scenarios were applied in an incompletely counterbalanced sequence: scenarios A and B (more continuous characteristic) alternated with scenarios C and D (more intermittent characteristic). The sequence was balanced within age and sex groups (Figure 3.1). Participants were informed about the initial and the last noise-free nights but had no knowledge about the dynamics of the different transportation noise scenarios. The scheduled sleep episode at habitual bedtime was 8 h in duration for every participant. The final awakening was either experimenter-induced (after the end of the 8 h sleep episode) or spontaneous (i. e., $\geq$ 3 min before the end of the 8 h sleep episode; 23.17 % of nights). Noise scenario playback started immediately after lights off and was without knowledge of the sleep stage. The reproduced sound in the bedroom was recorded continuously using a microphone and logged with the EEG recording device for time synchronization and verification. Participants spent days and nights in single windowless, soundproof, and temperature regulated bedrooms under constant ambient lighting levels (lux levels at the participant's eye during waking periods between 50 lux when sitting in bed and 150 lux when sitting at the table). Global subjective sleep quality was assessed every morning ("Taken everything together, how well did you sleep?"; scale 0-100). Noise annoyance for every single night was assessed en bloc in the morning of the last night ("How annoyed have you been during the respective night (1-6) by the noise?"; scale 0-100).

Prior to the study start, participants kept a regular sleep-wake cycle with self-selected habitual bedtimes and wake times for one week (nighttime sleep duration 8 h $\pm$ 30 min, no naptaking) as verified by accelerometers worn at the non-dominant wrist (Actiwatch AW4; Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep-logs. Additionally, participants were asked to restrict consumption of alcohol, caffeinated beverages, and chocolate to moderation during one week prior to the study in order to level out effects of these substances on sleep and waking functions.

A



B

Night 1	Night 2	Night 3	Night 4	Night 5	Night 6
NF	A	C	B	D	NF
NF	D	A	C	B	NF
NF	B	D	A	C	NF
NF	C	B	D	A	NF
NF	A	D	B	C	NF
NF	C	A	D	B	NF

Figure 3.1: Experimental protocol. (A) Schematic overview of the experimental protocol. Each nighttime episode was scheduled at the individual habitual bedtime (here, for illustrative purposes 24-8). Noise free baseline and recovery nights (light blue; hourly $L_{Aeq,1h}$ of 30 dB) always preceded resp. followed the different noise nights (dark blue; hourly $L_{Aeq,1h}$ of 45 dB). **(B)** The sequence of the different noise scenarios was incompletely counterbalanced and was designed according to the following rule: scenarios A and B (more continuous characteristic; shaded dark blue) alternated with scenarios C and D (more intermittent characteristic; dark blue). This sequence was balanced within age, sex, and genotype (for the young) groups.

2.3 Noise scenarios

Five prerecorded real-world inspired acoustical scenarios were played back in the bedroom during the night: one essentially noise-free (NF) and four transportation noise scenarios (Road A-C, Rail D; see Table 3.2). Throughout the paper, all reported acoustical metrics are based on A-weighted sound pressure levels (SPL). Scenario NF, played back during BL and RC nights, was designed to yield a constant hourly $L_{Aeq,1h}$ of 30 dB at the ear of the sleeper. It mimicked a rather tranquil real-world bedroom situation with a tilted window and very low transportation noise exposure. It consisted of sounds of crickets and of distant traffic. The four noise scenarios differed with respect to noise source (different road traffic situations and railway noise) and along a new acoustic exposure descriptor termed Intermittency Ratio (IR) (Wunderli et al., 2015), which characterizes the "eventfulness" of noise exposure situations. They were played back with a constant hourly equivalent continuous SPL, $L_{Aeq,1h}$, of 45 dB at the sleeper's ear. This approximately corresponds to an average outdoor façade level of 60 dB for a tilted window. Road scenario A represented a four-lane highway (speed limit of 120 km/h) with approximately 1,000 vehicles per hour at a distance of 400 m. Road scenario B represented a distance of 50 m from a two-lane country road (speed limit of 80 km/h) with approximately 250 vehicles per hour. Road scenario C represented a one-lane urban road (50 km/h) at a 15-m distance with approximately 100 vehicles per hour. Rail scenario D represented a railway noise situation with ten non-overlapping train pass-by events per hour.

Table 3.2: Characteristics of the acoustical scenarios

Scenario	Source	L_{Aeq} (dB)	L_{AFmax} (dB)	L_{A5} (dB)	L_{A10} (dB)	IR
A	road	45	53	49	48	0.3
B	road	45	60	52	48	0.7
C	road	45	62	52	48	0.8
D	rail	45	62	53	46	0.9
NF	"ambient/background"	30	39	35	34	0.3

Note. SPL refers to sound pressure level; L_{Aeq}: equivalent SPL; L_{AFmax}: maximum SPL; L_{A5}: SPL exceeded 5 % of the time; L_{A10}: SPL exceeded 10 % of the time; IR: Intermittency Ratio (Wunderli et al., 2015).

The sound stimuli were created by sound sampling, where recordings from single vehicle pass-bys were modified and mixed. Monophonic, calibrated sound recordings were taken outdoors under free-field conditions. The spectral effect of sound transmission through a tilted window was accounted for by using a digital filter that attenuated the high frequency content. For the road scenarios (A-C), realistic traffic was simulated using measured traffic flow statistics. For the rail scenario (D), five independent train pass-bys were recorded, four freight trains at 250 m and one commuter train 30 m from the track, and were played back with a pseudorandom equidistant spacing of 300 s. The transportation noise scenarios were designed to achieve the predefined level requirement in realistic and relevant exposure situations. Therefore, apart from transportation noise, they also contained the identical ambient noise from scenario NF.

The audio files were played back from portable audio devices (702T digital recorder, Sound Devices, Reedsburg, USA) through one active monitor loudspeaker (Focal CMS 50, Focal-JMlab, La Talaudière, France) at a distance of 2 m to the sleeper's head. Prior to the study start, the bedrooms were acoustically measured and calibrated using a sound level meter and by adjusting the playback volume.

To acoustically characterize the sound stimuli, acoustical metrics were calculated from the audio data in a post-hoc analysis. To that aim, the sound signals were first convolved with a measured room impulse response of the loudspeaker and the laboratory to consider the effects of the loudspeaker and the room acoustics on the reproduced sound at the sleeper's head. From these sound pressure signals, the A-weighted SPL history was calculated, from which several other metrics were derived (see Tables 3.2 and 3.3). The five railway noise events (RNE) differed with respect to event duration, maximum SPL (L_{AFmax}), sound exposure level (L_{AE}), and the maximum slope of the SPL (maxSPLslope; Table 3.3). A RNE started when the SPL exceeded a given threshold (here: 35 dB) and ended when the SPL fell below this threshold. The parameter maxSPLslope was determined based on regression lines fitted to the SPL (maximum slope of single regression lines fitted to 15 dB spreads of the SPL of a single RNE). In addition, the equivalent continuous SPL over 10 seconds ($L_{Aeq,10s,max}$) was calculated to assure compatibility of stimulus intensity with the literature (Buxton et al., 2012; Dang-Vu et al., 2010).

Table 3.3: Acoustical characteristics of the single railway noise events (scenario D)

Number	Duration (s)	L_{AFmax} (dB)	L_{AE} (dB)	L_{Aeq} (dB)	$L_{Aeq,10s,max}$ (dB)	MaxSPLslope (dB/s)
RNE1	52.1	50.1	62.4	45.2	48.4	1.0
RNE2	16.9	60.8	67.0	54.7	54.8	5.2
RNE3	63.6	60.9	71.2	53.2	56.1	1.7
RNE4	64.9	54.0	66.8	48.7	52.7	1.0
RNE5	113.7	61.7	75.0	54.5	60.6	0.7

Note. RNE refers to railway noise event; SPL: sound pressure level; duration: time when SPL is above threshold of 35 dB; L_{AFmax}: maximum SPL; L_{AE} : sound exposure level; L_{Aeq}: equivalent SPL; $L_{Aeq,10s,max}$: equivalent SPL over 10 seconds (maximum value); maxSPLslope: maximum slope during event (see text for calculation).

2.4 Sleep recording and outcome variables

The PSG comprised electroencephalogram (EEG), electromyogram (EMG), electrooculogram (EOG), and electrocardiogram (ECG) and was collected using a Vitaport-3 digital recorder (TEMEC Instruments B.V., Kerkrade, The Netherlands) with a sampling rate of 256 Hz (storage rate 128 Hz, 1.024 Hz for ECG signals). The EEG was recorded at twelve scalp sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2 according to the 10-20-electrode system referenced against averaged mastoids). The EOG was recorded from two electrodes that were placed at the outer canthi of both eyes with one electrode above and one below the horizontal. Submental EMG was recorded bipolarly. ECG was recorded with two electrodes placed at the center of the sternum and the left rib bone. Signals were filtered during recording (EEG, EOG, and ECG between 0.159-30 Hz; EMG between 1-70 Hz).

The PSG recordings were identified according to standard criteria by four experienced raters in our laboratory blind to the respective noise condition; inter-rater accordance was assured $> 85\,\%$. One scorer analyzed all six nights of one participant and the number of scored files was balanced according to the participant's sex and age. Scorers had regular scoring sessions to discuss questionable epochs and align local scoring procedures. Artifacts were rejected by visual inspection. Noisy or flat channels (on average more than 5 min of bad signal quality in total per night) were excluded from the analysis. In total, 246 nights were used: two nights were excluded due to technical problems. Signals were additionally offline-filtered between 0.5-32 Hz for visual scoring of sleep stages and EEG arousals. For sleep staging, the recommendations of the American Academy of Sleep Medicine (v2.3; Berry et al., 2016) were applied. In addition, SWS was further subdivided into NREM3 and NREM4: $\geq 50\,\%$ of slow wave activity per epoch according to Rechtschaffen and Kales (1968). For EEG arousal scoring, the recommendations of the American Sleep Disorders Association (Bonnet et al., 1992) were adopted; EEG arousal on- and offsets were determined. Time of awakenings–a sleep stage change from any sleep stage to wake–was pinpointed visually as re-occurrence of alpha or faster rhythms.

The following variables were included as outcome measures for sleep structure: total sleep time (TST), sleep efficiency (SE), onset latencies to NREM1, to NREM2, to SWS (i. e., first occurrence of respective sleep stage after lights off), and to REM (first occurrence of REM

after NREM2 onset), minutes spent in NREM1, NREM2, NREM3, NREM4, REM, and wake after sleep onset (i. e., time spent between sleep onset NREM1 and the final awakening in the morning), and the number of complete NREM-REM sleep cycles.

Sleep cycle definition based on a slight modification of the initial criteria proposed by Feinberg and Floyd (1979). NREM parts of a cycle (minimum duration of 20 min) comprised the time interval between NREM1 and successive REM onset (minimum duration of 5 min). However, for the first cycle different criteria were adopted: the first cycle started with NREM2 and the first REM part was allowed to be shorter than 5 min in duration. To account for omitted REM during the first cycle, the following criteria adopted from Jenni and Carskadon (2004) were introduced: for all episodes with first NREM part cycle duration $>$ 120 min, the first NREM part was divided into two, if SWS was interrupted by $>$ 12 min (i. e., every other sleep stage than SWS). Consequently, the first cycle ended with the last epoch of this interruption and the second started with the subsequent SWS onset. For cycle-related analyses, only completed cycles were included (i. e., end with REM sleep that was followed by at least 5 min of NREM sleep or wakefulness), that differed between participants and nights: $N = 32$ with 3 cycles, $N = 135$ with 4 cycles, $N = 68$ with 5 cycles, and $N = 11$ with less than 3 or more than 5 completed cycles.

Sleep continuity was assessed using the number and average duration of EEG arousals per hour of TST, the number and average duration of awakenings per hour of TST (final awakening excluded), the number of reciprocal NREM-REM transitions (NR: NREM-to-REM, RN: REM-to-NREM), and the total number of sleep stage changes per hour of TST.

2.5 Sleep spindle detection and outcome variables

Spindle detection followed a sequential two-step process: frequency peak identification by eye in the relevant spindle frequency range of all-night NREM power spectra (NREM2+SWS) with 9-12 Hz for slow spindles at averaged frontal derivations and 12-15 Hz for fast spindles at averaged centro-parietal derivations according to expected topographical distribution for slow and fast spindles (Mölle, Bergmann, Marshall, & Born, 2011) and spindle event detection. Individual spindle frequency peaks were used to account for profound inter-individual differences in spindle spectra (Buckelmüller, Landolt, Stassen, & Achermann, 2006; Werth, Achermann, Dijk, & Borbély, 1997). Power maxima in the fast spindle range were averaged over two nights (screening/adaptation night without any acoustical playback and the noise-free BL night) (fast spindle peak: young: 13.25 $\pm$ 0.48 Hz; older: 13.56 $\pm$ 0.74 Hz). Power maxima in the slow spindle range were identified in the noise-free BL night, but were not readily identifiable in nine participants (De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005; Werth et al., 1997) so the analysis was limited to fast spindles. Spindles were detected in artifact and arousal-free EEG segments during NREM sleep stages 2-4 (NREM2+SWS) using an automatic algorithm that adopted methodology proposed by Mölle, Marshall, Gais, and Born (2002). The SpiSOP toolbox is free, copyrighted software and is distributed and documented under www.spisop.org. In short, the root mean square (RMS) of each filtered EEG signal (band-pass filtered with $\pm$ 1.5 Hz around the individual fast frequency peak; -3 dB cutoff) was determined (window size of

0.2 s) and smoothed with a moving average (window size of 0.2 s). Spindles were detected by amplitude thresholding the RMS signal ($>$ 1.5 times the standard deviation of the filtered signal of the respective channel for 0.5-3 s).

Spindles were detected for all central and parietal derivations. The main outcome variable was the all-night spindle rate at EEG channel C3 during the noise-free BL night as this was originally used to relate spindle activity to arousal thresholds (Dang-Vu et al., 2010). Due to technical problems, for one participant C3 signal of one recording was bad and replaced by C4 as spindle rates did not differ significantly between hemispheres. Additional analyses also included parietal derivations as a topographically specific spindle impairment was reported in the older (Mander et al., 2014; N. Martin et al., 2013).The all-night spindle rate was calculated as number of detected spindle events per minute of NREM2+SWS. Additional spindle characteristics were determined: average duration (i. e., the time between threshold crossing in seconds), average oscillatory frequency (in hertz), and maximum amplitude (peak-to-peak difference in microvolt) during NREM2+SWS. All outcomes were also calculated for each NREM sleep cycle to account for age-dependent differences in spindle activity over consecutive NREM sleep cycles (Guazzelli et al., 1986; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Purcell et al., 2017) and during NREM2 and SWS only to test differences between sleep stages.

2.6 Event-related cortical activations: arousability from RNEs

Due to its highly intermittent characteristic, for the railway noise scenario (scenario D), cortical activations could be related to distinct, well-defined pass-by events. For the other three scenarios, the event-related analysis was not possible due to a more continuous temporal variation of the SPL. Cortical activation probabilities (i. e., awakening probability and EEG arousal probability) were calculated as ratios between the number of noise associated awakenings/EEG arousals and the number of adequate noise events. A cortical activation was considered noise associated if it occurred within the time span of the particular RNE. Noise events were considered inadequate if the respective onset met one of the following three criteria: occurrence prior to the first sleep onset of NREM2, occurrence during intra-sleep wakefulness, awakening in 30 seconds or EEG arousal in 10 seconds prior to noise onset (Marks et al., 2008; McGuire et al., 2016). The longer the scanned window (here, event duration), the higher the probability that a spontaneous, non-noise-associated EEG arousal is attributed to this window so that the spontaneous arousal probability might not be comparable between the different noise events whose duration differed greatly. Thus, in addition to cortical activation probabilities, cortical activation rates were calculated as ratio between the number of noise associated awakenings/EEG arousals and the duration of adequate noise events. In sum, 3,360 RNEs were applied; 2,840 events contributed to the analysis (15.48 % were excluded based on the aforementioned exclusion criteria; mean exposure time per participant: 70.86 min; 35.69 min non-arousal associated RNEs during NREM2+SWS).

“Virtual” events (i. e., periods during the two noise-free nights with the same duration and distribution across the night as during the RNE scenario subjected to the same aforementioned

exclusion criteria) (Basner et al., 2011; Griefahn, Brode, et al., 2008; McGuire et al., 2016) were used for two purposes: to determine spontaneous cortical activation probabilities and to test the effect of noise exposure (Pivik et al., 1999; Sato et al., 2007) on spindle characteristics with comparing exposure (during RNE duration) to non-exposure periods (during "virtual" event duration). Exposure vs. non-exposure comparisons were restricted to NREM events and to non-EEG arousal/awakening associated events to not confuse effects of noise and EEG arousal/awakening on spindle characteristics. In total, 3,280/3,120 "virtual" events (BL/RC) were considered; 2,769/2,590 events were used for analysis (15.58/16.99 % were excluded; mean "exposure" time per participant: 70.91/69.32 min; 39.05/37.07 min non-arousal associated events during NREM2+SWS).

2.7 Statistical analyses

All subjective sleep quality, sleep, and spindle outcomes were analyzed using linear mixed-effects models with a random intercept for the participant, the within-participant factor noise scenario (1+4+1 different noise nights), the between-participant factor age group (young and older), and the interaction between the two factors. Planned orthogonal contrasts were used to test the difference between the pooled two noise-free nights and pooled four noise exposure nights, the pooled noise-free nights and the individual noise exposure nights, and finally, the first and the last night to test the effect of the time in the experiment on all outcome variables; each contrast testing was done in separate for both age groups. Stratified analyses were performed for individuals with a low and a high spindle rate (based on the median all-night spindle rate during NREM2+SWS of individual means over all centro-parietal derivations during the noise-free nights) to test whether noise exposure modified sleep structure and continuity differently in these two spindle groups. The spindle rate (means over all centro-parietal derivations during the noise-free nights) was also correlated with other person self-report measures that might play a role in sleep quality: self-reported noise sensitivity (LEF-K, NoiSeQ subscale Sleep), trait anxiety (STAI), and self-reported sleep quality (PSQI). Correlations were derived using Pearson correlation coefficients. Additional factors (apart from noise and the age group) were included in the model for a detailed analysis of the effects of the spindle rate, the NREM sleep cycle, or acoustical characteristics of single RNEs: for the sake of clarity, these factors will be described in the respective result paragraphs.

For the event-related analyses, logistic regression models with a participant-specific random intercept were used to test the effect of the C3 BL all-night spindle rate (as well as separate models for all other derivations) on EEG arousal and awakening probability from single RNEs. Acoustical (maximum SPL, maxSPLslope), sleep-related (sleep stage prior to threshold exceedance of the SPL: NREM1 vs. NREM2, SWS vs. NREM2, and REM vs. NREM2, sleep cycle since sleep onset, study night), and subject variables (age group: young vs. older, sex: female vs. male) were included. To test whether the effect of spindles, that showed marked reduction with aging (Crowley et al., 2002; Knoblauch et al., 2005; Mander et al., 2014; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Nicolas et al., 2001; Purcell et al., 2017; Warby

et al., 2014), is independent of the age group, three separate models were fitted: one model including only the BL spindle rate, a second model that included both the BL spindle rate and the age group, and a third model that only included the age group. If the effect of the BL spindle rate is significant in a model controlled for age (Model 2), this might be indicative of an indirect (mediating) effect of the BL spindle rate for the relationship between age and EEG arousal probability (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). In addition, model fit comparisons were used to select the better predictor (age group or BL spindle rate) for EEG arousal probability using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) with the lowest value indicative of the superior model. To account for the divergent temporal dynamics of spindle activity and cortical activation probabilities across successive NREM cycles, cortical activation probabilities and spindle activity were correlated within each NREM cycle, separately for both age groups. For this, the analysis was restricted to NREM cortical activations as spindles are characteristic for NREM sleep.

All analyses were performed in R (R Core Team, 2018). Mixed models were fitted with lme4::lmer via the *afex package* (v0.18-0; Singmann, Bolker, Westfall, & Aust, 2017). Denominator degrees of freedoms for all effects were approximated using the Kenward-Rogers procedure. Type 3 sums of squares were used. Post-hoc tests and planned contrasts were run using the *lsmeans* package (v2.26-3; Lenth, 2016): p-values were adjusted using an approximation of the Dunnett or the Tukey adjustment, depending on the type of comparison. Logistic regression models were fitted using lme4::glmer (v1.1-13; Bates, Mächler, Bolker, & Walker, 2015) and model non-convergence issues were solved by centering continuous predictor variables. The alpha level was set to $p < 0.05$.

3 Results

3.1 Sleep structure and continuity

Noise effects and interaction with age. Noise exposure increased the number of arousals (especially during NREM sleep) and the number of total sleep stage changes (planned contrasts of the pooled two noise-free nights with the pooled four noise exposure nights; all $p < 0.05$, Dunnett's test; Tables 3.5 and 3.6 in the Supplement). In the older individuals, sleep was more fragmented under noise exposure than in noise-free nights as indicated by an increase in the number of NREM EEG arousals, the number of awakenings from NREM sleep, the amount of NREM1, and the number of total sleep stage changes. According to planned contrasts between the noise-free nights and the individual noise nights, the noise effects were mainly driven by the road scenarios B and C. In the young subgroup, however, pooled noise exposure decreased the latency to REM and increased amounts of REM sleep without any clear indication of differences for the single noise nights. But, these effects can only partially be attributed to the noise as they also demonstrated time-in-study effects (see following paragraphs).

Age effects. Minutes in intra-sleep wake and NREM stages 1-2, total number of arousals per hour TST (during NREM and REM), awakenings per hour TST (particularly from NREM), total number of sleep stage changes, the number of reciprocal NREM-REM transitions, and the latency to SWS were significantly higher in the older compared to the young group, while total sleep time, sleep efficiency, and minutes in SWS were significantly lower (Tables 3.5 and 3.6).

Time-in-study effects. REM-related variables showed a time-in-study effect with a decrease in latency, an increase in the number of NREM-REM transitions and the duration of REM arousals throughout the protocol for both age groups. Additionally, the young subgroup showed an increase in REM sleep, in the duration of NREM arousals, and latency to NREM2 over the course of the protocol (planned contrasts between the first and the last experimental night; all $p < 0.05$, Dunnett's test; results are shown in the last column of Tables 3.5 and 3.6).

3.2 Sleep spindles

Sleep spindle characteristics (during NREM2+SWS), noise effects, and interaction with age. When controlling for EEG derivation, all-night *spindle rate* was stable across noise nights for the young individuals (all planned contrasts not significant with $p > 0.05$, Dunnett's test; Figure 3.2 for EEG derivations C3 and P3; analyses based on all three derivations of central and parietal positions), but decreased during noise nights compared to the noise-free nights for older individuals what was present in all scenarios but road noise scenario B ($p < 0.05$, Dunnett's test). *Spindle duration* decreased upon noise exposure in both age groups and was significantly reduced in the young individuals upon noise exposure in all scenarios but train scenario D ($p < 0.05$, Dunnett's test). *Spindle amplitude* showed consistently significant differences between the pooled noise-free and the pooled noise nights in both age groups: maximum spindle amplitude was significantly reduced during exposure of road scenarios A and B ($p < 0.05$, Dunnett's test). *Spindle frequency* was stable across noise nights for both age groups ($p < 0.05$, Dunnett's test). All interactions with the EEG derivation were non-significant.

The additional within-participant factor cycle (up to 5 factor levels for the number of sleep cycles) was included in the model. For *spindle rate* per minute NREM2+SWS at C3, post-hoc tests for the significant interaction between age and cycle ($F_{4,882.56} = 64.00, p < 0.001$) revealed that the rate increased progressively across sleep cycles until cycle 4 in the young subgroup (best fitted by a simple linear trend) and was fairly stable in the older subgroup (pair-wise post-hoc comparisons largely insignificant, except for the first cycle that demonstrated a higher spindle rate; P3 had the same results; Figure 3.3). Spindle rate differences between age groups increased across the night and were maximal during the fourth NREM cycle.

Sleep spindle characteristics, age effects, and interaction with topography. We observed a reduction in spindle rate in older as compared to young individuals what was particularly present at central when compared to parietal derivations (interaction between topography (central and parietal) and age ($F_{1,444} = 61.63, p < 0.001$). Spindle duration was significantly reduced

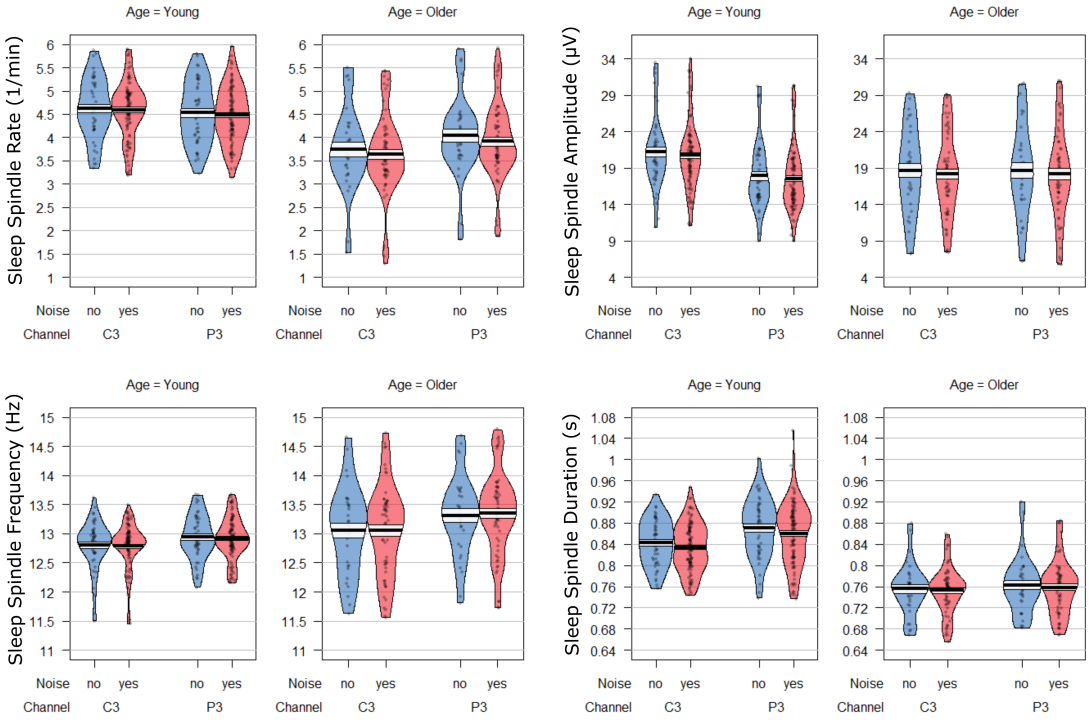


Figure 3.2: Sleep spindle characteristics (NREM2+SWS). Sleep spindle characteristics (NREM2+SWS) for the different noise conditions. Noise "no" denotes noise-free nights (pooled for baseline and recovery night) and Noise "yes" denotes noise nights (pooled for all four different noise nights). Characteristics are plotted as a RDI plot (Raw, Description, and Inference): the raw data were jittered horizontally, the bean indicates the underlying distribution, the superimposed line denotes the mean, and the rectangle denotes the standard error.

in older when compared to young individuals ($F_{1,40.12} = 36.47, p < 0.001$) and both groups had longer spindles at parietal as compared to central derivations ($F_{1,444} = 86.31, p < 0.001$). Spindle amplitude was lower at central but not parietal derivations in the older compared to the young and spindle amplitude was higher at central than at parietal derivations in the young but not the older (post-hoc testing of the significant interaction between age and topography ($F_{1,444} = 111.11, p < 0.001$). The spindle frequency, however, was not significantly different between age groups, but was higher at parietal than central derivation in both age groups what was more pronounced in the older (post-hoc testing of the significant interaction between age and topography ($F_{1,444} = 34.13, p < 0.001$).

Sleep spindle rate and sleep structure and continuity. Planned contrasts within the two spindle groups (low vs. high based on the median all-night spindle rate) on all sleep structure and continuity outcomes failed to reveal any consistent differences between spindle groups, except for an increase in latency to NREM1 in the low spindle rate group of the older individuals during road scenario A. Across all nights, irrespective of the noise, higher spindle rates during NREM2+SWS were associated with longer NREM2 duration ($p < 0.001$, 18.30 min increase

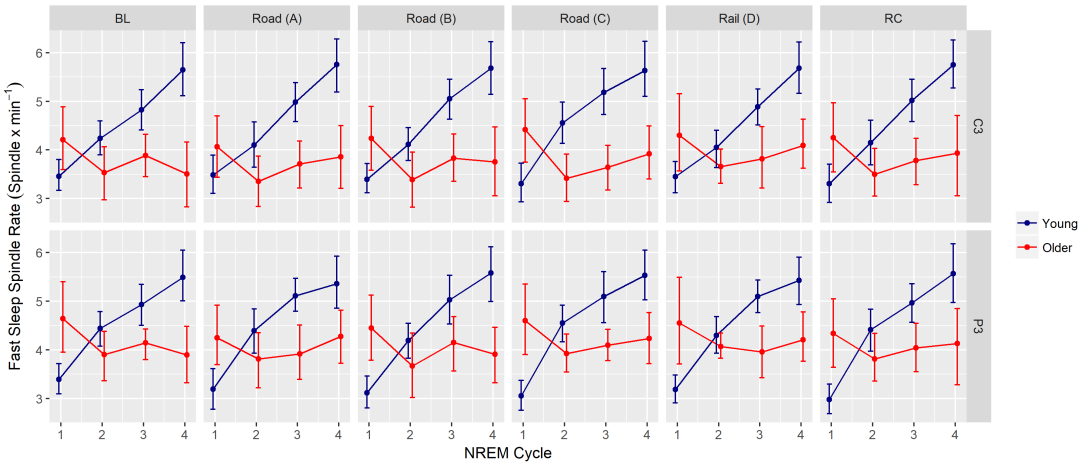


Figure 3.3: Sleep spindles across successive NREM cycles. Sleep spindle rates for derivations C3 and P3 during NREM2-4 are shown across successive four NREM cycles according to noise exposure for young ($N = 26$) and older participants ($N = 16$): mean $\pm$ 95 % confidence intervals. Individual nights were excluded if the number of completed cycles was different than 3, 4, or 5 ($N = 11$). Individual cycles were only included if they were completed (i. e. end with REM sleep that was followed by at least 5 minutes of NREM sleep or wakefulness) to account for within-cycle variation of the spindle rate.

per unit in spindle rate) and fewer number of awakenings per hour TST ($p = 0.048$, 0.28 n/h TST decrease per unit spindle rate) in mixed models with the additional continuous variable spindle rate (all-night NREM2+SWS spindle rate during the respective night averaged over all centro-parietal derivations). In addition, higher spindle rates coincided with fewer number of arousals ($p = 0.009$, 4.17 n/h TST decrease per unit spindle rate) in the older and shorter NREM4 duration ($p < 0.001$, 17.23 min decrease per unit spindle rate) in the young individuals.

Sleep spindle rate and subjective variables. Noise reduced global subjective quality of sleep ($F_{5,167.21} = 3.70, p = 0.003$), irrespective of age: this was mirrored in the planned contrasts of the noise-free nights for the pooled noise exposure and for all road noise exposure nights on the individual noise contrast level ($p < 0.05$, Dunnett's test). Noise exposure was perceived as annoying ($F_{5,190.17} = 20.48, p < 0.001$), irrespective of age: annoyance was significantly higher for all noise exposure nights (for pooled exposure as well as on the individual noise contrast level) compared to the noise-free nights. Spindle rates (averaged over all centro-parietal derivations) during noise-free nights were not correlated with change in subjective sleep quality (between combined noise and noise-free nights: $r = -0.03, p = 0.868$) or with change in noise annoyance (between combined noise and noise-free nights: $r = -0.12, p = 0.468$). Lastly, the spindle rates during the noise-free nights were not significantly correlated to any tested person characteristic: self-reported noise sensitivity (LEF-K: $r = -0.08, p = 0.634$; NoiSeQ subscale Sleep: $r = -0.05, p = 0.752$); trait anxiety (STAI: $r = 0.20, p = 0.210$); or self-reported sleep quality (PSQI:$r = -0.24, p = 0.133$).

Sleep spindle characteristics during noise exposure. Spindle rates during exposure compared to non-exposure periods were not significantly different. The additional model factor single RNE (5 different noise events), however, revealed that the spindle rates were related to acoustical characteristics of the single RNEs. There was a significant interaction between the factor noise (yes/no) and single RNE ($F_{4,358.06} = 4.69, p = 0.001$): post-hoc tests revealed that this effect was driven by noise event RNE2 (among the loudest with a maximum SPL of 60.8 dB and with the highest maxSPLslope of 5.2 dB/s; Table 3 for event characteristics), that caused a significant reduction in spindle rates on all tested centro-parietal derivations, similarly for both age groups (Figure 3.4A). Corroborating our earlier reported all-night findings, spindle amplitude was significantly reduced during exposure compared to non-exposure periods in both age groups (present in all derivations but more pronounced at central derivations). Exposure vs. non-exposure spindle amplitude differences, however, were not related to any acoustical characteristic of the event.

3.3 Event-related cortical activations: arousability from RNEs

NREM cortical activation probabilities from single railway noise events varied quite considerably between individuals and ranged from 1.89 up to 53.66 % for EEG arousal (mean ± SD probability: 26.55 ± 12.81 %) and between 0 and 12.50 % for awakening (mean ± SD probability: 4.05 ± 3.61 %). After adjusting for a range of relevant contributing parameters (Basner et al., 2011; Griefahn, Brode, et al., 2008; Marks et al., 2008), awakening probability from single

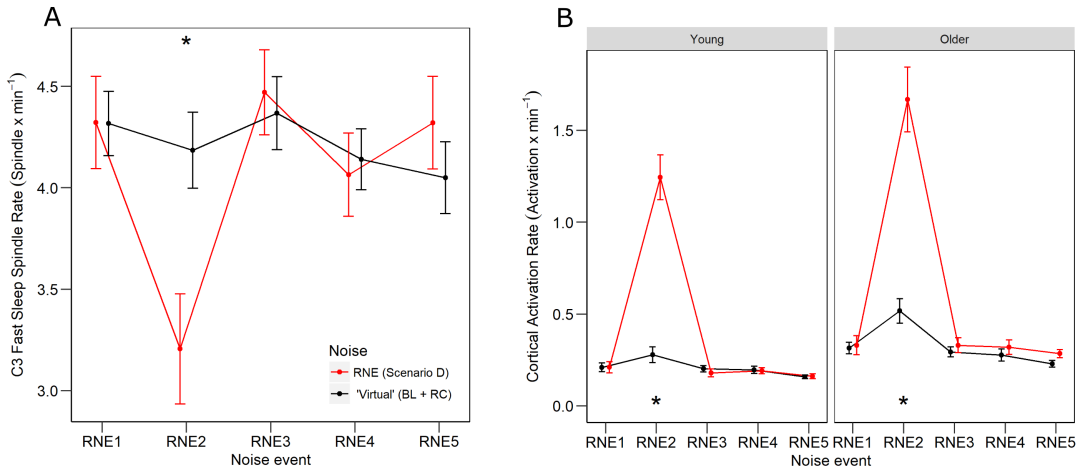


Figure 3.4: Effects of single RNE on sleep spindle rates and cortical activation rates. (A) C3 spindle rate during exposure ($N = 1414$ RNE; red) and non-exposure ($N = 3022$ "virtual" events; black) periods during NREM2+SWS. Events have different acoustical characteristics (Table 3). Selected intervals of "virtual" events during the noise-free nights (baseline: BL, recovery: RC) had the same duration and distribution as single RNEs in the railway night (scenario D). Here, events were only included if not associated with an awakening or an EEG arousal. **(B)** Cortical activation rates (EEG arousal and awakening rates combined) for all (i. e. NREM an REM events) railway ($N = 2840$ events; red) and "virtual" ($N = 5359$; black) noise events.* Significant with $p < 0.05$, Tukey's test.

railway noise events was not significantly related to all-night BL spindle activity (Table 3.4; same results for all other centro-parietal derivations). Awakening probability increased with maximum SPL, sleep cycle, and with prior sleep stage NREM1 when compared to NREM2. For EEG arousal probability from single RNEs, all-night BL spindle activity only contributed significantly to the model when it was not adjusted for age: as soon as the age predictor was included, all-night BL spindle activity lost predictive value (Table 3.4; same results for all other centro-parietal derivations). Consequently, there was no indication of an indirect effect of the BL spindle rate on the relationship between age and EEG arousal probability. Both used performance metrics (AIC and BIC) indicated that Model 3 was the superior model, including only the age group. EEG arousal probability increased with maximum SPL, maximum SPL slope, sleep cycle, older age and was significantly higher from NREM1 and significantly lower from SWS when compared to NREM2.

As there was no effect of the all-night, trait-like spindle rate on EEG arousal probability from RNEs, we further explored state effects of the spindle rate taking inter- and intra-individual differences in the spindle rate across sleep cycles into account. The correlations (within-cycle, within-age group) between the same-night spindle rates and NREM EEG arousal probabilities were largely non-significant (the two significant correlations indicated two positive relationships in the young individuals); thus, inter-individual differences in the spindle rate were not inversely related to NREM EEG arousal probabilities, not only on the all-night but also on the level of the sleep cycle (Figure 3.5). In the aforementioned logistic model (excluding the sleep cycle as a factor), the sleep cycle-specific spindle rate did not significantly influence EEG arousal probability (both with and without the age factor; for all EEG derivations; $p > 0.05$; data not shown).

The further exploration of the significant acoustical factors revealed a significant interaction between noise (yes/no) and single RNE (5 different events) for the cortical activation rate (EEG arousal and awakening rate combined for REM and NREM events) ($F_{4,360} = 80.47, p < 0.001$). Post-hoc tests revealed that this effect was driven by noise event RNE2 (among the loudest with a maximum SPL of 60.8 dB and with the highest maxSPLslope of 5.2 dB/s; Table 3.3 for event characteristics), that had significantly higher noise-associated cortical activation rates than spontaneous cortical activation rates (for "virtual" events; Figure 3.4B). The significant interaction between single RNE and age ($F_{4,360} = 3.68, p = 0.006$) indicated that older individuals had a higher increase in cortical activation rates for the noise events RNE2 and RNE3 (both among the loudest) than young individuals.

4 Discussion

The present analyses sought to investigate the sleep-protective role of sleep spindles under different nighttime transportation noise exposures. While sleep structure was largely unaffected by noise exposure, sleep continuity was disrupted in an age- and noise scenario-dependent manner. Older individuals, whose sleep is generally more fragmented, had an increased frequency of NREM EEG arousals, both spontaneous and event-related, and awakenings from NREM.

Table 3.4: Results of logistic regression models for event-related awakening and EEG arousal from single railway noise events (scenario D)

	Awakening		EEG arousal		
Variable	Model 1	Model 2	Model 1	Model 2	Model 3
Intercept	-0.4490 (0.2105)***	-3.3807 (0.2395)***	-1.2491 (0.1436)***	-1.5484 (0.1578)***	-1.5376 (0.1471)***
LAFmax (dB)	0.0859 (0.0267)**	0.0862 (0.0268)**	0.0470 (0.0113)***	0.0469 (0.0113)***	0.0469 (0.0113)***
Maximum slope (dB/s)	0.0195 (0.0564)	0.0193 (0.0565)	0.0853 (0.0287)**	0.0855 (0.0288)**	0.0855 (0.0287)**
Prior sleep stage NREM1 (vs. NREM2)	1.1299 (0.2598)***	1.1374 (0.2603)***	1.5243 (0.1574)***	1.5184 (0.1574)***	1.5173 (0.1573)***
Prior sleep stage SWS (vs. NREM2)	-0.2350 (0.3829)	-0.2524 (0.3841)	-1.0364 (0.1852)***	-1.0075 (0.1853)***	-1.0073 (0.1853)***
Prior sleep stage REM (vs. NREM2)	0.1613 (0.2492)	0.1565 (0.2494)	0.1942 (0.1091)	0.2018 (0.1091)	0.2017 (0.1091)
Sleep cycle	0.1874 (0.0783)*	0.1847 (0.0785)*	0.0679 (0.0379)	0.0714 (0.0379)*	0.0717 (0.0378)*
Study night (day)	0.0037 (0.061)	0.0031 (0.0606)	0.0171 (0.0489)	0.0197 (0.0428)	0.0197 (0.0428)
Male sex (1 = yes, 0 = no)	-0.2472 (0.2408)	-0.2639 (0.241)	0.2208 (0.1890)	0.2873 (0.1669)	0.2825 (0.1650)
Spindle rate (n/min NREM2+SWS)	-0.0812 (0.1488)	-0.1251 (0.1675)	-0.2346 (0.1131)*	0.0236 (0.1240)	
Older age (1 = yes, 0 = no)		-0.1559 (0.2779)		0.7245 (0.2113)***	0.7003 (0.1688)***
Variance random subject (SD)	0.1598 (0.3998)	0.1531 (0.3913)	0.2742 (0.5236)	0.1886 (0.4343)	0.1887 (0.4344)

Note. Regression coefficients with standard errors in parenthesis. The dependent variable in these analyses is awakening/EEG arousal probability that is coded with 0 = no awakening/EEG arousal and 1 = awakening/EEG arousal. To address model non-convergence issues, all continuous predictor variables were centered at their respective mean: L_{AFmax}: 57.58 dB; MaxSPLslope: 1.90 dB/s; Sleep cycle: 2.84; Study night: 2.44 nights; Spindle rate (at C3 during the noise-free baseline night): 4.28 n/min NREM2+SWS. Model fit for model 1 ($AIC = 2907.39$; $BIC = 2972.40$), model 2 ($AIC = 2898.98$; $BIC = 2969.89$), and model 3 ($AIC = 2897.01$; $BIC = 2962.02$). $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

They had more total sleep stage changes and spent more time in NREM1, especially in nights under road noise exposure (scenarios B and C). Contrary to our hypotheses, spindle activity was neither related to differences in sleep structure or continuity in noise exposure nights nor was it a significant predictor for cortical activation probabilities from single RNEs. And, cortical activation probability that increased throughout the night was not related to naturally occurring variation in spindle rate over successive NREM sleep cycles. Spindle amplitude, on the other hand, was consistently decreased during noise compared to noise-free nights across all EEG

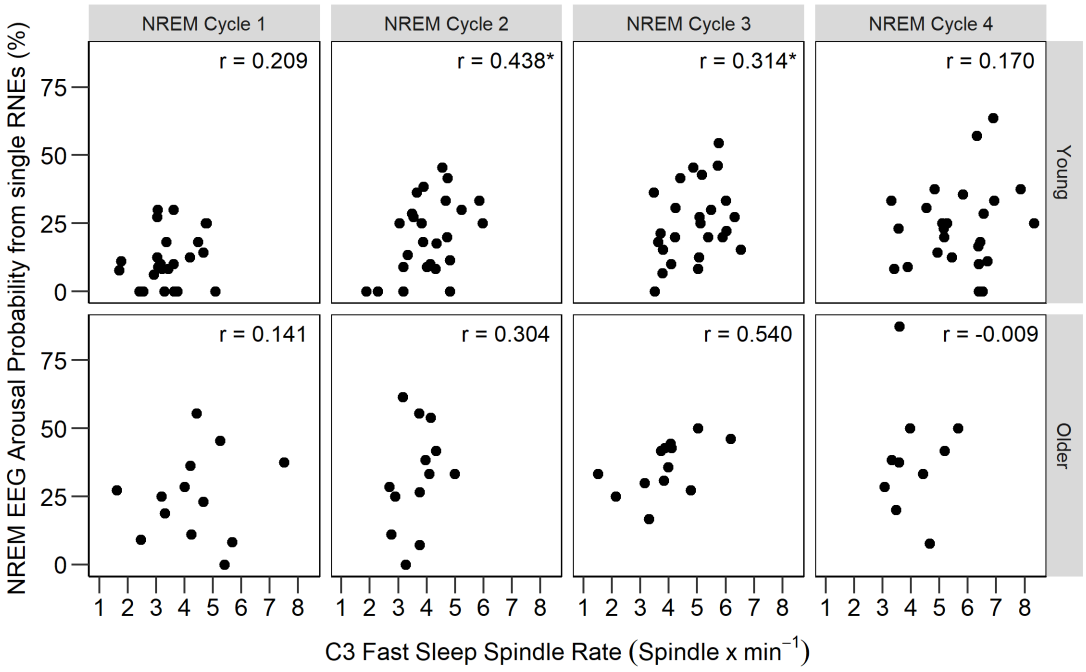


Figure 3.5: Sleep spindle rates and arousal probabilities from single RNE across successive NREM cycles. Within-cycle correlations between the NREM EEG arousal probability from single RNE and the same-night C3 spindle rate are shown. The young participants ($N = 25$) are displayed in the upper and the older participants ($N = 13$) in the lower panels. Individual nights were excluded if the number of completed cycles was different than 3, 4, or 5 ($N = 4$) and individual cycles were only included if completed (i. e. end with REM sleep that was followed by at least 5 minutes of NREM sleep or wakefulness) to account for within-cycle variation of the spindle rate. * Significant with $p < 0.05$.

derivations and age groups, both in the all-night analyses and during selected intervals of noise exposure compared to non-exposure in the event-related analysis.

At first glance, our results seem to contradict Dang-Vu et al. (2010), who demonstrated that arousal thresholds were related to all-night baseline spindle rates in a sample of young adults with a mean age of 26.3 years. But, arousal thresholds differ from arousal probabilities such that the former describes the sound intensity needed to elicit an arousal, whereas the latter describes the percentage of arousal-associated noise events. Arousal thresholds in Dang-Vu et al. (2010) were determined using a series of 10-second events with increasing intensity (5-dB increments starting at 40 dB) until an arousal occurred or the maximum intensity of 70 dB was reached. Our experimental procedure did not include on-line stimulation adjustments as predefined real-world inspired noise scenarios were played back during the night with a limited maximum SPL range between 50.1 and 61.7 dB (all starting from a background level of 30 dB). Depending on the applied acoustical metric, the maximum intensity in our stimuli was about 10 dB (for the equivalent continuous metric $L_{Aeq,10s,max}$ and approx. 17 dB for the maximum SPL) lower than the maximum intensity used by Dang-Vu et al. (2010) but was well within the range of their mean arousal threshold per individual (40-60 dB) and within the range people are exposed to under real-life conditions during the nighttime (Federal Office for the Environment,

2009) The slope of rise of the SPL and the duration of single noise events influence cortical activation probabilities (Basner et al., 2011; Brink et al., 2008; Marks et al., 2008). These are acoustical parameters that varied in our experiment but were held constant in Dang-Vu et al. (2010). Moreover, it was demonstrated that the arousal probability depends on the type of the presented sound: electronic sounds, such as phone ringing, consistently exceeded arousal probability from transportation noise by far for all tested sound pressure levels with a constant slope of rise of the SPL (Buxton et al., 2012). We do not question the role of sleep spindles for differential information processing of very brief stimuli that was repeatedly shown (Cote et al., 2000; Dang-Vu et al., 2011; Elton et al., 1997; Schabus et al., 2012) but argue that mechanisms other than sleep spindle activity alone may play a role under real-life exposure conditions when arousability also depends on the meaning and significance of stimuli (Blume et al., 2017; Oswald, Taylor, & Treisman, 1960). For our single RNEs, cortical activation probability depended on the maximum SPL and the maximum slope of the SPL. Steep rising SPL of single noise events are indicative of a fast approaching noise source and therefore signal a potential threat to the sleeping individual. Indeed, it was demonstrated that activity in the amygdala–functioning as a detector of biologically relevant stimuli (Sander, Grafman, & Zalla, 2003)–was increased for rising SPL stimuli as compared to falling SPL stimuli during wakefulness (Bach et al., 2008). Consequently, other markers of the sympathetic tone during sleep denote the importance of the slope of rise of the SPL: the steeper the slope of rise of a single noise event, the greater the heart rate elevation (Griefahn, Brode, et al., 2008), systolic and diastolic blood pressure increase (N. Carter et al., 2002), or motility as measured with high-resolution actigraphy (Brink et al., 2008).

In addition to the evaluation of all-night inter-individual differences in spindle rates, within-individual and within-night differences can be used to predict arousability. Spindle rates vary across successive NREM cycles in an age-dependent manner: while fast spindle rate increases linearly across cycles 2-4 in the young, it is rather stable in the older; except for the first cycle that has higher spindle rates in both age groups (Purcell et al., 2017; Wei et al., 1999). If spindles are sleep-protective, cycle-specific intra-night variability in spindle rates should affect arousal probabilities, both event-related and spontaneous. But, the linear increase in spindle rates across successive NREM cycles in the young was accompanied by an increase rather than a decrease in arousal probability from single RNEs. The increase of event-related arousal probability reflects a sleep-homeostatic reduction of sleep consolidation consistent with the literature (Basner et al., 2011; Griefahn, Brode, et al., 2008; Marks et al., 2008). Interestingly, in the older, the fairly stable spindle rate across cycles was also accompanied by an increase in arousal probability across the night. In the same vein, Pivik et al. (1999) demonstrated that within-night differences in the spindle rate on an even finer temporal scale, 2-minute pre-exposure, were not consistently predictive for awakening probabilities or awakening thresholds (i. e., stimulus intensity needed to elicit awakening). In mice, on the other hand, phase differences in a 0.02-Hz oscillation in sigma power (frequency range of 10-15 Hz), were associated with awakening from sleep in response to 20-s auditory stimuli: awakening occurred when the sigma power was in the

descending phase during noise exposure as compared to non-awakening when sigma power was in the ascending phase (Lecci et al., 2017).

We observed a stimulus intensity-dependent decrease of spindle rates during noise exposure in the absence of overt cortical activations: 61 dB sound stimuli with a high maximum slope of the SPL reduced spindle rates by approx. 20 % when compared to "virtual" events. In the same vein, Kawada and Suzuki (1994) showed that truck pass-bys also resulted in a decrease of spindle rates as compared to pre-exposure spindle rates, which recovered as a function of the stimulus intensity: spindle rates upon 55 dB exposure recovered faster than 60 dB and 65 dB exposure that recovered to pre-exposure levels only after three min. Pivik et al. (1999) showed that repetitive stimulation with artificial 3-s sounds was accompanied by a significant decrease of spindle rates during noise exposure as compared to pre-exposure rates what was also more pronounced with increasing stimulus intensity. In other studies, auditory stimulation did not affect spindle rates (Church et al., 1978) or even triggered spindle generation: upon white noise stimulation in the spindle frequency range (Antony & Paller, 2017) or during selected intervals of auditory stimulation compared to NREM2 periods without auditory stimulation during an afternoon nap (Sato et al., 2007). In the latter, however, stimulus intensities of the used auditory stimuli were at the individual's awake perception threshold, therefore much lower than in our experiment.

The observed all-night and event-related decrease in spindle amplitude might be interpreted as a disruption of synchronization of TC oscillation and was also demonstrated by others where auditory stimulation sequences of 50-ms-click sounds resulted in a reduction of spindle power when compared to sham stimulation (Weigenand, Mölle, Werner, Martinetz, & Marshall, 2016). It has long been noticed that sensory stimulation can elicit K-complexes (KCs) (Davis et al., 1939), single slow oscillations that occur predominately during NREM2 sleep, even in the absence of overt cortical activations. Auditory evoked KCs (either isolated or followed by a spindle or a burst of additional KCs or slow waves) were followed by a 50 % reduction of EEG power in the 13-14 Hz frequency band (a surrogate for spindle activity that is even stronger correlated with the mean spindle amplitude than the spindle rate) (Purcell et al., 2017) which was interpreted as an inhibition of spindle generation (Halasz, 1993). The observed all-night reduction in spindle amplitude might be due to a cumulative evoked KC or EEG arousal effect what needs to be demonstrated in future analyses.

Overall, we did not find an independent effect of spindles on a variety of sleep structure and continuity markers of noise disturbed sleep (using average sound levels of 45 dB and maximum sound levels of 50-62 dB) after controlling for age. Spindle rates were lower and sleep was more fragmented in the older compared to the young individuals. The overall and topographically specific spindle reduction in the older is consistent with the literature (Crowley et al., 2002; Knoblauch et al., 2005; Mander et al., 2014; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Nicolas et al., 2001; Purcell et al., 2017; Warby et al., 2014) and was related to differences in white matter integrity of the underlying spindle generating networks (Mander, Winer, & Walker, 2017). Sleep spindles are trait-like transitory EEG oscillations, which may reflect stable sleep but do not necessarily protect the sleeper against external stimuli such as nighttime

transportation noise. Arousal thresholds are lower during SWS compared to NREM2 sleep (Basner et al., 2011; Busby et al., 1994; Marks et al., 2008; Roehrs et al., 1994) and whether marked age-related differences in slow-wave activity or characteristics of slow oscillations modify noise effects on sleep will be demonstrated in future analyses. The reduction in spindle amplitude, however, might serve as a sensitive marker for noise-induced sleep disturbances. Meanwhile, biologically relevant acoustical characteristics of single noise events, such as the slope of rise of the SPL, may play an important role in modifying information processing even during intact spindle rhythmicity.

Limitations

Our automatic spindle detection algorithm potentially suffers from the well-described caveats for automatic detection, such as a lower performance in older individuals compared to the gold-standard, human visual detection (Warby et al., 2014). To address this issue, amplitude thresholds were adjusted individually as EEG power densities in the frequency ranges of slow-waves, theta and sigma are lower in older than in young individuals (Carrier et al., 2001; Dijk, Beersma, & van den Hoofdakker, 1989). On the other hand, reduced spindle rates with advancing age is a robust finding demonstrated using both visual (N. Martin et al., 2013) and automatic (Crowley et al., 2002; Knoblauch et al., 2005; Nicolas et al., 2001; Purcell et al., 2017; Warby et al., 2014) detection.

Two types of sleep spindles were described from cortical EEG recordings with differences in frequency and topographical distribution, that suggest distinct functional roles (Schabus et al., 2007). We only analyzed fast spindles as slow spindle peaks were not readily identifiable in the majority of our participants. Slow spindles could have modified sleep differently, though it is not very likely as demonstrated by Dang-Vu et al. (2010).

Table 3.5: Sleep structure and continuity according to respective noise exposure in the young individuals ($N = 26$)

Variable	Noise-free (pooled)	Noise (pooled)	Road (A)	Road (B)	Road (C)	Rail (D)	N6-N1
Total sleep time (min)	452.27 ± 17.89	455.88 ± 16.09	457.67 ± 15.57	455.33 ± 17.13	454.60 ± 17.98	455.83 ± 14.42	2.84 ± 21.00
Sleep efficiency (%)	94.22 ± 3.73	94.98 ± 3.35	95.35 ± 3.24	94.86 ± 3.57	94.71 ± 3.74	94.96 ± 3.00	0.59 ± 4.37
Sleep latency NREM 1 (min)	10.70 ± 8.46	9.83 ± 7.57	8.94 ± 6.62	10.82 ± 7.45	10.36 ± 9.76	9.23 ± 6.48	**5.61 ± 10.39**
Sleep latency NREM 2 (min)	18.17 ± 10.25	16.69 ± 9.32	14.88 ± 8.22	16.15 ± 8.25	17.78 ± 10.54	18.02 ± 10.34	**9.86 ± 10.01**
Sleep latency SWS (min)	32.06 ± 14.86	28.57 ± 9.67	25.42 ± 7.57	28.36 ± 8.73	29.99 ± 10.07	30.63 ± 11.60	6.46 ± 17.85
Sleep latency REM (min)	76.28 ± 29.34	**65.98 ± 22.05**	65.62 ± 23.31	68.46 ± 27.47	65.02 ± 16.42	64.75 ± 20.25	**-28.64 ± 35.81**
WASO (min)	13.55 ± 13.19	12.85 ± 11.98	11.54 ± 12.15	11.73 ± 9.79	14.17 ± 13.15	14.06 ± 13.07	-4.73 ± 15.62
NREM 1 (min)	58.45 ± 15.51	56.36 ± 15.51	54.90 ± 15.99	56.31 ± 11.54	56.96 ± 16.07	57.31 ± 18.49	2.07 ± 17.41
NREM 2 (min)	215.65 ± 30.42	215.24 ± 30.28	219.08 ± 31.49	215.17 ± 30.06	211.5 ± 31.50	214.92 ± 29.46	**-18.41 ± 30.54**
NREM 3 (min)	37.68 ± 9.24	38.18 ± 10.73	38.35 ± 10.72	38.08 ± 9.69	40.00 ± 12.22	36.44 ± 10.61	0.39 ± 12.24
NREM 4 (min)	41.17 ± 27.41	39.94 ± 28.54	38.83 ± 27.86	42.12 ± 30.62	38.79 ± 27.68	39.92 ± 29.38	1.14 ± 18.43
REM (min)	99.33 ± 20.87	**106.17 ± 22.93**	106.52 ± 22.73	103.65 ± 23.47	107.35 ± 22.63	107.23 ± 24.00	**17.66 ± 22.37**
Sleep Cycles (N)	4.31 ± 0.55	4.23 ± 0.61	4.19 ± 0.63	4.31 ± 0.62	4.08 ± 0.65	4.31 ± 0.55	0.23 ± 0.53
EEG Arousal rate (n/h TST)	10.07 ± 3.52	10.71 ± 3.72	10.74 ± 3.60	10.83 ± 4.39	0.83 ± 3.77	10.44 ± 3.24	0.44 ± 2.52
EEG Arousal rate (n/h NREM)	9.42 ± 4.03	10.17 ± 4.05	10.10 ± 4.13	10.22 ± 4.73	10.63 ± 3.86	9.76 ± 3.56	-0.27 ± 2.83
EEG Arousal rate (n/h REM)	12.37 ± 5.82	12.75 ± 5.90	13.18 ± 6.04	12.92 ± 6.38	11.75 ± 5.76	13.06 ± 5.63	3.11 ± 4.81
EEG Arousal duration (s)	10.82 ± 1.58	10.61 ± 1.60	10.62 ± 1.70	10.66 ± 1.45	10.26 ± 1.34	10.88 ± 1.87	**0.83 ± 1.48**
EEG Arousal duration NREM (s)	10.93 ± 1.65	**10.58 ± 1.73**	10.57 ± 1.84	10.78 ± 1.47	**10.08 ± 1.50**	10.86 ± 2.01	**0.58 ± 1.58**
EEG Arousal duration REM (s)	10.58 ± 2.67	11.15 ± 2.87	11.21 ± 2.55	10.94 ± 2.94	11.11 ± 2.73	11.33 ± 3.34	**1.63 ± 2.31**
Awakening rate (n/h TST)	1.53 ± 1.00	1.54 ± 0.86	1.47 ± 0.75	1.53 ± 0.88	1.55 ± 0.72	1.60 ± 1.08	-0.47 ± 1.25
Awakening rate (n/h NREM)	1.43 ± 1.14	1.45 ± 0.90	1.36 ± 0.83	1.39 ± 0.80	1.44 ± 0.78	1.62 ± 1.17	-0.60 ± 1.24
Awakening rate (n/h REM)	1.93 ± 1.83	1.87 ± 1.73	1.79 ± 1.65	2.16 ± 1.97	1.94 ± 1.71	1.60 ± 1.62	-0.07 ± 2.17
Awakening duration (min)	1.12 ± 0.59	1.09 ± 1.23	0.86 ± 0.49	0.96 ± 0.38	1.46 ± 2.34	1.12 ± 0.60	0.00 ± 0.57
Awakening duration NREM (min)	1.23 ± 0.72	1.13 ± 1.30	0.92 ± 0.53	1.01 ± 0.51	1.46 ± 2.42	1.17 ± 0.87	-0.03 ± 0.6
Awakening duration REM (min)	0.80 ± 0.48	1.16 ± 2.48	0.66 ± 0.26	0.81 ± 0.52	1.75 ± 4.16	1.52 ± 2.83	0.22 ± 0.59
NR transitions (n/h TST)	2.04 ± 0.94	2.12 ± 0.81	2.14 ± 0.91	2.04 ± 0.77	2.01 ± 0.77	2.27 ± 0.81	**0.66 ± 0.84**
RN transitions (n/h TST)	1.64 ± 0.96	1.73 ± 0.80	1.74 ± 0.85	1.63 ± 0.82	1.59 ± 0.66	1.93 ± 0.87	**0.59 ± 0.97**
Total sleep stage changes (n/h TST)	19.00 ± 4.48	19.40 ± 4.15	19.03 ± 4.33	19.40 ± 3.33	19.41 ± 4.44	19.77 ± 4.61	-0.69 ± 3.25

Note. Means ± standard deviations. A-D: different noise scenarios with indicated noise source and different values for the Intermittency Ratio; TST: total sleep time; NR: NREM-to-REM transition; RN: REM-to-NREM transition; N6-N1: difference between the last (N6) and the first (N1) night of the protocol; Highlighted in bold text: significant difference for respective contrast with the two noise-free nights: either with the pooled noise nights, the single noise nights, or the last night ($p < 0.05$, Dunnett's test).

Table 3.6: Sleep structure and continuity according to respective noise exposure in the older individuals ($N = 16$)

Variable	Noise-free (pooled)	Noise (pooled)	Road (A)	Road (B)	Road (C)	Rail (D)	N6-N1
Total sleep time (min)	415.28 ± 34.87	422.59 ± 34.99	421.06 ± 46.20	415.5 ± 36.95	426.44 ± 27.40	427.38 ± 28.20	**-25.88 ± 30.78**
Sleep efficiency (%)	86.52 ± 7.26	88.04 ± 7.29	87.72 ± 9.62	86.56 ± 7.70	88.84 ± 5.71	89.04 ± 5.87	**-5.39 ± 6.41**
Sleep latency NREM 1 (min)	10.88 ± 6.06	10.80 ± 8.81	12.37 ± 14.60	10.98 ± 6.28	10.05 ± 5.11	9.79 ± 6.57	**4.69 ± 5.57**
Sleep latency NREM 2 (min)	16.07 ± 7.64	16.43 ± 9.64	17.06 ± 14.52	18.14 ± 9.03	15.02 ± 6.02	15.48 ± 7.45	3.38 ± 8.38
Sleep latency SWS (min)	44.69 ± 31.22	43.38 ± 29.32	46.91 ± 30.78	40.45 ± 14.93	36.87 ± 17.46	49.29 ± 45.07	3.19 ± 34.78
Sleep latency REM (min)	71.77 ± 28.87	64.44 ± 22.86	64.69 ± 22.59	62.00 ± 16.83	63.69 ± 14.57	67.38 ± 34.26	**-24.59 ± 34.56**
WASO (min)	38.20 ± 19.66	42.45 ± 29.43	43.28 ± 34.46	50.16 ± 34.32	41.84 ± 25.33	34.53 ± 22.34	0.22 ± 27.67
NREM 1 (min)	79.28 ± 25.24	**84.49 ± 28.23**	79.75 ± 28.67	**87.41 ± 32.19**	**87.59 ± 27.23**	83.22 ± 26.48	-7.44 ± 20.86
NREM 2 (min)	212.30 ± 37.24	**221.16 ± 34.70**	227.12 ± 43.40	212.69 ± 31.55	224.03 ± 30.92	220.78 ± 33.14	**-23.59 ± 26.1**
NREM 3 (min)	27.95 ± 21.74	25.55 ± 17.96	22.59 ± 16.92	28.56 ± 19.68	24.88 ± 16.41	26.16 ± 19.78	2.84 ± 10.17
NREM 4 (min)	5.64 ± 8.94	5.00 ± 7.27	6.22 ± 7.84	3.78 ± 5.78	5.94 ± 9.09	4.06 ± 6.27	-0.91 ± 8.66
REM (min)	90.11 ± 26.07	86.40 ± 24.7	85.38 ± 25.49	83.06 ± 23.94	84.00 ± 20.77	93.16 ± 28.98	3.22 ± 28.28
Sleep Cycles (N)	4.06 ± 1.05	4.25 ± 1.07	4.25 ± 1.00	4.25 ± 1.00	4.31 ± 1.25	4.19 ± 1.11	0.25 ± 1.06
EEG Arousal rate (n/h TST)	18.51 ± 8.63	19.43 ± 8.61	18.79 ± 9.01	20.20 ± 9.22	19.14 ± 8.32	19.59 ± 8.63	1.35 ± 3.97
EEG Arousal rate (n/h NREM)	17.26 ± 8.73	**18.47 ± 8.77**	17.80 ± 9.39	**19.50 ± 9.53**	18.36 ± 8.12	18.23 ± 8.75	0.79 ± 4.10
EEG Arousal rate (n/h REM)	24.13 ± 14.64	24.17 ± 14.58	23.95 ± 16.97	24.25 ± 15.84	22.94 ± 14.39	25.52 ± 11.97	2.80 ± 11.53
EEG Arousal duration (s)	10.84 ± 1.92	10.75 ± 1.77	10.66 ± 1.86	10.66 ± 1.33	10.88 ± 2.27	10.81 ± 1.65	**0.77 ± 1.41**
EEG Arousal duration NREM (s)	10.42 ± 1.98	10.40 ± 1.79	10.32 ± 1.70	10.35 ± 1.33	10.52 ± 2.33	10.41 ± 1.82	0.42 ± 1.47
EEG Arousal duration REM (s)	12.00 ± 2.83	11.99 ± 2.58	11.89 ± 3.04	12.03 ± 2.95	12.18 ± 2.57	11.87 ± 1.84	**1.19 ± 1.89**
Awakening rate (n/h TST)	2.26 ± 0.88	**2.65 ± 1.28**	2.60 ± 1.24	2.71 ± 1.24	2.75 ± 1.26	2.54 ± 1.49	-0.05 ± 1.04
Awakening rate (n/h NREM)	2.39 ± 1.00	**2.78 ± 1.45**	2.63 ± 1.37	2.86 ± 1.51	2.97 ± 1.44	2.67 ± 1.60	-0.01 ± 1.29
Awakening rate (n/h REM)	1.86 ± 1.64	2.13 ± 1.86	2.51 ± 1.98	2.13 ± 2.08	1.81 ± 1.49	2.07 ± 1.94	-0.24 ± 1.74
Awakening duration (min)	2.76 ± 1.57	2.48 ± 1.72	2.65 ± 2.52	2.86 ± 1.69	2.35 ± 1.19	2.08 ± 1.20	0.30 ± 2.14
Awakening duration NREM (min)	2.76 ± 1.84	2.77 ± 2.26	2.96 ± 3.30	3.39 ± 2.49	2.57 ± 1.35	2.14 ± 1.26	0.65 ± 2.53
Awakening duration REM (min)	2.28 ± 3.22	1.85 ± 4.09	2.65 ± 3.66	1.09 ± 0.91	0.76 ± 0.55	2.89 ± 7.24	0.40 ± 1.28
NR transitions (n/h TST)	2.96 ± 1.49	2.74 ± 1.39	**2.49 ± 1.51**	2.89 ± 1.50	2.61 ± 1.22	2.97 ± 1.37	**0.97 ± 1.28**
RN transitions (n/h TST)	2.65 ± 1.52	**2.36 ± 1.35**	**2.08 ± 1.40**	2.48 ± 1.45	2.30 ± 1.26	2.59 ± 1.34	**0.86 ± 1.40**
Total sleep stage changes (n/h TST)	27.73 ± 7.51	**29.58 ± 8.31**	27.79 ± 8.5	30.09 ± 8.22	**30.17 ± 7.66**	**30.26 ± 9.32**	**3.19 ± 4.65**

Note. Means ± standard deviations. A-D: different noise scenarios with indicated noise source and different values for the Intermittency Ratio; TST: total sleep time; NR: NREM-to-REM transition; RN: REM-to-NREM transition; N6-N1: difference between the last (N6) and the first (N1) night of the protocol; Highlighted in bold text: significant difference for respective contrast with the two noise-free nights: either with the pooled noise nights, the single noise nights, or the last night ($p < 0.05$, Dunnett's test).

Chapter 4

Ultradian modulation of EEG arousals during sleep: effects of age and exposure to nighttime transportation noise

Authors

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Contributions

FR, LT contributed to data collection; FR, SF, LT, CC performed the analysis; FR wrote the manuscript; LT, RP, HH, ICE, MF, DV, MB, JMW, NPH, MR, SF, CC provided fruitful interpretation of the data; FR, LT, RP, JMW, MB, MF, DV, NPH, MR, CC designed the data acquisition protocol; RP created and analyzed the acoustical stimuli; all authors participated in the revision of the manuscript.

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ABSTRACT

Study Objectives

The present study aimed at assessing the temporal NREM EEG arousal distribution within and across sleep cycles and its modifications with aging and nighttime transportation noise exposure, two factors that typically increase the incidence of EEG arousals.

Methods

Twenty-six young (19-33 years, 12 women) and 16 older (52-70 years, 8 women) healthy volunteers underwent a repeated measures polysomnographic six-day laboratory study. Participants spent two noise-free nights and four transportation noise exposure nights, two with continuous and two characterized by eventful noise (average sound levels of 45 dB, maximum sound levels between 50 and 62 dB for eventful noise). Generalized mixed models were used to model the time course of EEG arousal rates during NREM sleep and included cycle, age, and noise as independent variables. Supplementary analyses explored the contributing role of slow wave sleep (SWS).

Results

Arousal rate variation within NREM sleep cycles was best described by a u-shaped course with variations across cycles. Older participants had higher overall arousal rates than the younger individuals with differences for the first and the fourth cycle depending on the age group. During eventful noise nights, overall arousal rates were increased compared to noise-free nights. Additional analyses suggested that the arousal rate time course was partially mediated by SWS.

Conclusions

The characteristic u-shaped arousal rate time course indicates phases of reduced physiological sleep stability both at the beginning and end of NREM cycles. Small effects on the overall arousal rate by eventful noise exposure suggest a preserved physiological within- and across-cycle arousal evolution with noise exposure, while aging affected the shape depending on the cycle.

1 Introduction

Transient activation phases during sleep (i. e., autonomic arousals, sleep stage changes, cortical arousals, or awakenings) are generally considered to fragment sleep and, as a result, negatively impact the recuperative value of sleep (Bonnet & Arand, 2003; S. E. Martin et al., 1996, 1997; Stepanski, 2002; Wesensten et al., 1999). Transient activation phases can occur in response to external stimuli, such as transportation noise (Basner, Glatz, et al., 2008; Basner et al., 2011; Marks et al., 2008; Rudzik et al., 2018; Saremi et al., 2008; Smith et al., 2017) or high-intensity white noise (Nakagawa, 1987; Scott, 1972; Terzano et al., 1990). They also increase with aging without external stimuli and are part of the normal aging process in humans (Bonnet & Arand, 2007; Boselli et al., 1998; Klerman et al., 2013; Terzano et al., 2002; Yetton, McDevitt, Cellini, Shelton, & Mednick, 2018). However, besides their potential negative effect on sleep continuity, transient activation phases are also an integral and essential characteristic in the ultradian time course of physiological sleep (Akerstedt et al., 2002; Bonnet & Arand, 2007; Halasz et al., 2004).

Cortical arousals, as one class of transient activation phases during sleep, are not distributed randomly, but tend to cluster around certain time points during sleep (Halasz et al., 2004; Terzano & Parrino, 2000; Terzano et al., 2000). Typically, sleep is organized in 4-5 ultradian sleep cycles of 90-110 minutes, each which comprise an episode of non-rapid eye movement (NREM) sleep followed by an episode of rapid eye movement (REM) sleep (Feinberg & Floyd, 1979). Temporal variations of cortical arousals can therefore be examined on the level of the sleep cycle (within-cycle) as well as over the course of an entire night sleep period (across-cycle). So far, these variations were almost exclusively investigated within the framework of the cyclic alternating pattern (CAP), a marker of sleep instability (Parrino, Ferri, Bruni, & Terzano, 2012; Terzano & Parrino, 2000) but insufficiently for the most established marker for cortical arousal: EEG arousal defined according to the rules of the American Academy of Sleep Medicine (AASM) (Berry et al., 2016).

CAP is a rhythmic NREM EEG pattern characterized by sequences of A and B phases: EEG activity during A phases is either synchronized (subtype A1), desynchronized (subtype A2), or mixed (subtype A3), with the latter two overlapping with EEG arousals; B phases are composed of EEG background activity (Parrino et al., 2012; Terzano & Parrino, 2000). Regarding the time course, it was observed that subtypes A2 and A3 occur more frequently during the ascending (i. e. when sleep is more superficial and progressing towards REM) than the descending (i. e. the first part of the ultradian sleep cycle when sleep progresses from lighter to deeper sleep) part of a sleep cycle (Halasz et al., 2004; Terzano & Parrino, 2000; Terzano et al., 2000). Intra-night variations of spontaneous number of EEG arousals per hour have primarily been examined across sleep cycles while detailed time course analyses within sleep cycles have not yet been investigated. Results suggest no variation of EEG arousals across cycles (Sforza et al., 2008) or time elapsed since sleep onset (De Gennaro et al., 2001). Spontaneous EEG arousals occur more frequently from both stage 1 NREM (N1) and REM sleep compared to stage 2 NREM sleep (N2) and slow wave sleep (SWS); EEG arousal rates are generally lowest during SWS

(De Gennaro et al., 2001; Sforza et al., 2008). Within-cycle evolution of slow-wave activity (SWA) follows an inverted u-shaped pattern with a gradual buildup, a plateau phase and a rapid decline towards the transition to REM sleep depending on time asleep during the night (Aeschbach & Borbély, 1993; Dijk et al., 1993; Merica & Gaillard, 1986) suggesting that the underlying arousal and SWS generating mechanisms might be antagonistic. Across the night sleep period, however, the gradual decrease of SWA across cycles (Achermann & Borbély, 1997; Cajochen et al., 1994; Dijk et al., 1993) does not mirror the across-cycle stability of EEG arousal (Sforza et al., 2008) suggesting that EEG arousals are not a good marker for sleep homeostasis. Taking the two perspectives into consideration, namely transient activation phases as a marker for sleep fragmentation and as an integral and essential characteristic of physiological sleep, we were interested in modelling the EEG arousal time course and its modifications with aging and nighttime transportation noise exposure.

We analyzed the microstructural architecture of NREM sleep using EEG arousals as a marker for transient activation phases. Data were acquired in a sample of healthy young and older individuals that underwent a six-day polysomnographic (PSG) laboratory study and had two noise-free and four noise exposure nights (four different noise exposure situations: two with continuous and two characterized by eventful noise). To model the time course of EEG arousals, we normalized the NREM episodes of a cycle by subdividing it into ten parts of equal length (within-cycle effect) and did this for the first four cycles across the night sleep period (across-cycle effect). The aim of the paper was threefold. First, we were mainly interested in modelling the time course of EEG arousals both within and across sleep cycles, which we expected to vary in a u-shaped pattern within cycles but not across cycles. Second, we investigated age-related modifications of temporal EEG arousal distributions. All-night number of EEG arousals per hour increase with aging (Bonnet & Arand, 2007; Boselli et al., 1998), but it is unclear how within- and across-cycle dynamics differ between age groups. Third, building on the notion that transportation noise increases the number of all-night EEG arousals (Basner et al., 2011; Saremi et al., 2008), we were interested whether EEG arousals during noise exposure nights had a similar temporal distribution pattern than during undisturbed nights. It is currently unknown whether the additional EEG arousals during noise nights occur at the same or other, additional time points than those of the physiological EEG arousal time course.

2 Methods

2.1 Participants

Data of forty-two healthy volunteers in two age groups (26 young: 24.6 $\pm$ 3.5 years, 19-33 years, 12 women; 16 older: 60.8 $\pm$ 5.9 years, 52-70 years, 8 women) were included for analyses; two participants of the older group dropped out of the experiment due to medical reasons (data excluded), and two participants of the young group dropped out after four nights due to personal reasons (data included). All participants were free from any acute or chronic illness and current medication (as assessed by means of clinical history, physical examination by

a study physician, and routine blood and toxicological urine testing; young women without hormonal contraceptive use) and had good sleep (habitual sleep duration per night 8 $\pm$ 1 h; normal subjective sleep quality (Pittsburgh Sleep Quality Index (Buysse et al., 1989), PSQI $\leq$ 5); normal general daytime sleepiness (Epworth Sleepiness Scale (Johns, 1991), ESS $\leq$ 10); and no signs of sleep disorders, such as sleep-related movement and breathing disorders as confirmed via PSG during one screening/adaptation night prior to study admission. All had normal sex- and age-appropriate hearing thresholds (maximum hearing loss of the better ear no greater than the 10th percentile of an otologically normal population (International Organization for Standardization, 2000) at the frequencies 250, 500, 1000, 2000, 3000 and 4000 Hz) tested manually with an audiometer (Bosch ST-10, Stuttgart, Germany).

The study protocol, screening questionnaires, and consent forms were approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, Switzerland, #2014-121) and conformed to the tenets of the Declaration of Helsinki. All participants gave written informed consent prior to study participation and received financial compensation for participation. Data acquisition took place between October 2014 and June 2016.

2.2 Protocol and procedure

The protocol comprised six consecutive nights and days in the sleep laboratory. All participants were exposed to four different transportation noise scenarios that were played back during four nights with an incompletely counterbalanced sequence: scenarios with a more continuous noise characteristic (Road A-B) were alternated with scenarios with a more eventful noise characteristic (Road C, Rail D). Participants spent two noise-free nights that were always the first (baseline night: BL) and the last night (recovery night: RC). Participants were informed about the initial and the last noise-free nights but had no knowledge about the dynamics of the different transportation noise scenarios. Time in bed was scheduled at individuals' habitual bedtime and lasted 8 hours for every participant. Noise scenario playback started immediately after lights off. Days and nights were spent in single windowless, soundproof, and temperature regulated bedrooms (22°C) under constant ambient lighting levels during waking periods (between 50-150 lux at the participant's eye).

Participants were asked to keep a regular sleep-wake cycle with self-selected habitual bed and wake times for one week prior to the study start (nighttime sleep duration 8 $\pm$ 0.5 h, no nap taking). Compliance was verified by accelerometers worn on the non-dominant wrist (Actiwatch AW4; Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep-logs. During one week prior to the study start, they were also asked to restrict consumption of alcohol, caffeinated beverages, and chocolate to moderation to level out effects of these substances on sleep and waking functions. Young women were generally tested during the early follicular phase of their menstrual cycle (one woman was tested during the late luteal phase and progressed to the follicular phase over the course of the experiment; another woman was during the luteal phase for the whole experiment).

2.3 Noise scenarios

We used five pre-recorded real-world inspired acoustical scenarios for playback in the bedroom during the night: one essentially noise-free (NF) and four transportation noise scenarios (Road A-C, Rail D) that differed with respect to noise source (different road traffic situations and railway noise) and noise exposure situation (more continuous, more eventful). Scenario NF ($L_{Aeq,1h}$ of 30 dB at the ear of the sleeper; represents a rather tranquil real-world bedroom situation with a tilted window and distant road traffic plus natural sounds) was played back during BL and RC nights. Transportation noise scenarios ($L_{Aeq,1h}$ of 45 dB at the ear of the sleeper; corresponds to an average outdoor façade level of 60 dB for a tilted window) were designed to represent relevant exposure situations (Table 4.1). Road A represented a four-lane highway (speed limit of 120 km/h) with approximately 1,000 vehicles per hour at a distance of 400 m. Road B represented a distance of 50 m from a two-lane country road (speed limit of 80 km/h) with approximately 250 vehicles per hour. Road C represented a one-lane urban road (50 km/h) at a 15-m distance with approximately 100 vehicles per hour. Rail D represented a railway noise situation with ten non-overlapping freight and passenger train pass-by events per hour. Creation of acoustical scenarios has been previously described in detail (Rudzik et al., 2018).

Table 4.1: Characteristics of the acoustical scenarios

Scenario	Noise source	Noise type	L_{Aeq} (dB)	L_{AFmax} (dB)	L_{A5} (dB)	L_{A10} (dB)
A	road	continuous	45	53	49	48
B	road	continuous	45	60	52	48
C	road	eventful	45	62	52	48
D	rail	eventful	45	62	53	46
NF	ambient/background	noise-free	30	39	35	34

Note. SPL refers to sound pressure level; L_{Aeq}: equivalent continuous A-weighted SPL; L_{AFmax}: maximum SPL with time weighting FAST; L_{A5}: SPL exceeded 5 % of the time; L_{A10}: SPL exceeded 10 % of the time.

The noise scenarios were classified as three types with each factor representing two nights: noise-free (BL and RC night), continuous noise exposure (Road A and B), and eventful noise exposure (Road C and Rail D). Road C included 400 single road noise events that differed according to duration (16.6-58.8 s), maximum sound pressure level (SPL) (52.6-62.4 dB), and maximum slope of the SPL (2.4-6.4 dB/s). Rail D included 80 single railway noise events that differed according to duration (16.9-113.7 s), maximum SPL (50.1-61.7 dB), and maximum slope of the SPL (0.7-5.2 dB/s). Noise events were distributed equally across the night (see Supplement 1.1.2).

The audio files were played back from portable audio devices (702T digital recorder, Sound Devices, Reedsburg, USA) through an active monitor loudspeaker (Focal CMS 50, Focal-JMlab,

La Talaudière, France) at a 2-m distance to the sleeper's head. The sound reproduction chain was calibrated with a sound level meter (Nor-121, Norsonic, Norway).

All reported acoustical metrics are based on A-weighted SPL.

2.4 Sleep recording

The PSG was recorded on Vitaport-3 digital recorder (TEMEC Instruments B.V., Kerkrade, The Netherlands) with a sampling rate of 256 Hz (storage rate 128 Hz, 1.024 Hz for ECG signals). The EEG was recorded at twelve scalp sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2 according to the 10-20-electrode system referenced against averaged mastoids). The electrooculogram (EOG) was recorded from two electrodes that were placed at the outer canthi of both eyes with one electrode above and one below the horizontal. The submental electromyogram (EMG) was recorded bipolarly. The electrocardiogram (ECG) was recorded with two electrodes placed at the center of the sternum and the left rib bone. Signals were filtered during recording (EEG, EOG, and ECG between 0.159-30 Hz; EMG between 1-70 Hz). Sleep staging and EEG arousal scoring followed the standard criteria of the AASM (v2.3; Berry et al., 2016) and was conducted by four experienced raters, blind to the specific noise exposure.

2.5 Sleep cycles

Definition of sleep cycles were largely based on standard criteria (Feinberg & Floyd, 1979) with NREM episodes of a cycle (minimum duration: 20 min) being the time between the first epoch of N1 and the subsequent REM onset ($\geq$ 5 min). In the first cycle, the minimum REM duration was allowed to be shorter than 5 min. Occasionally, a skipping of the first REM episode is observed: where REM is expected (i. e., after a consolidated period of SWS), only a lightening of the sleep process (i. e., a sleep stage transition to N1 or a brief awakening) occurs, especially during the first night in a new environment (Agnew, Webb, & Williams, 1966) or in younger individuals (Jenni & Carskadon, 2004). A NREM episode of a cycle was divided into two episodes if it was $>$ 120 min in duration (wakefulness excluded) and SWS was interrupted by $>$ 12 min by any other sleep stage than SWS (Jenni & Carskadon, 2004; Kurth et al., 2010). Consequently, the second cycle started with the subsequent SWS onset. We included only the first four cycles (Sforza et al., 2008) that were complete, i. e. where REM sleep was followed by at least 5 minutes of NREM or wakefulness and only nights with at least three and not more than five completed cycles (see Figure 4.1). Consequently, sleep epochs after the last REM part and before the final awakening were neglected as were episodes after the fourth cycle. In most cases, the final awakening was experimenter-induced (after the end of the 8-hour sleep period) and not spontaneous ($\geq$ 3 min before the end of the 8-hour sleep period; 23.17 % of nights). In total, 234 nights were analysed (33 nights with three, 134 with four, and 67 nights with five completed cycles), while 12 nights needed to be excluded (for 11 nights, the number of completed cycles was less than three or more than five; in one night, REM latency was less than 15 min). From a total of 903 cycles, 48 (5.31 %) were excluded: 4 (0.44 %) because the REM episode was $<$ 5 min for cycles 2-4 and 44 (4.87 %) because the cycle duration was outlying

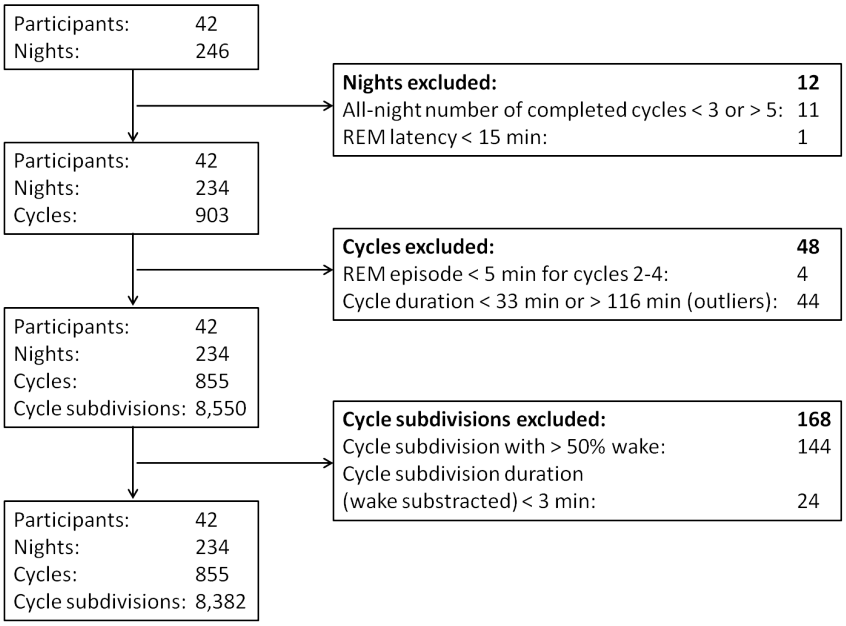

Figure 4.1: Flow diagram of the selection of nights, cycles, and cycle subdivisions.

short or long, based on a cycle duration shorter or longer than the upper/lower quartile $\pm$ 1.5 times the interquartile range of the cycle duration (see Supplement 1.1.3). The median NREM episode length of the 855 sleep cycles was 70 minutes.

2.6 Outcome variables

Analysis of sleep macro- and microstructure variables was restricted to the first four sleep cycles. Sleep macrostructure variables included total sleep time (TST), sleep efficiency (SE), onset latencies to N1, N2, SWS (i. e., first occurrence of respective sleep stage after lights off), and REM (first occurrence of REM after N2 onset), percentage of TST spent in intra-sleep wake, N1, N2, SWS, and REM (i. e., all for the episodes between N1 onset and the final awakening in the morning). Sleep microstructure variables included EEG arousal rates (n/h TST, n/h NREM, and n/h REM) as well as awakening rates (n/h TST, n/h NREM, and n/h REM).

As differences between NREM and REM sleep EEG arousals are to be expected (Peter-Derex et al., 2015), we limited the analyses to NREM sleep and only modelled within- and across-cycle effects during NREM episodes. Each NREM episode of a sleep cycle was divided in ten parts of equal length (based on the scoring window duration of 0.5 min; if the quotient was uneven, duration of this cycle subdivision was 1/10 NREM part + 0.5 min which was assigned randomly). The dependent variable was the EEG arousal rate during each cycle subdivision (CSD), modelled by the number of EEG arousals per CSD and an offset (the logarithm of CSD length). In addition, SWS was calculated as percentage of time spent in SWS per CSD duration (% of CSD duration). From a total of 8,550 CSDs, 168 (1.96 %) were excluded (144 (1.68 %)

because of $> 50\,\%$ wake in CSD; 24 (0.28 %) when CSD length corrected for wakefulness was shorter than 1/10 of the minimum cycle duration of all individuals).

2.7 Statistical analyses

For statistical analyses of standard sleep variables, linear mixed models were used, which included random subject effects to account for the repeated measurements within participants. We included factors for noise type (noise-free vs. eventful noise vs. continuous noise), age group (young vs. older), and the interaction between the two.

We used generalized linear mixed models (GLMM) to fit the time course of arousal rates per CSD. The distribution of arousal rates was highly skewed to the left due to the absence of any EEG arousal in 45.38 % of the CSDs (see Supplement 1.1.3). The distribution did not suggest any transformation to achieve normality and did not comply with a Poisson distribution. Thus, we opted for a negative binomial distribution, an alternative to the Poisson distribution used to model data that contain many zeros. Details of the statistical modelling and all intermediate steps are documented in the Supplement. We started with a simple model with only the main effects, the offset, and a random subject effect and explored residual variances with respect to different discrete distributions. The main effects and only factors considered were age group (young vs. older), noise type (noise-free vs. eventful noise vs. continuous noise), cycle (1 to 4), and CSD (1 to 10). Next, we evaluated orthogonal polynomial time trends regarding their ability to represent the 10-level-within cycle effect with fewer parameters. After this, we explored all possible two-way interactions and added them to the model, whenever likelihood-ratio tests indicated significance of the included two-way interaction. In the resulting model with all fixed effects specified, we first addressed possible collinearity between the fixed effects, as well as residual variance heterogeneity and time related error structures. In a final step, we explored whether the resulting model could be simplified.

To address the first aim, the modelling of the within- and across-cycle time course of EEG arousal rates, we evaluated the two main effects of CSD and cycle, as well as their interaction. To address our second aim, the modification with age, we evaluated the main effect of age as well as the possible interaction of age with CSD and cycle. A significant interaction between age and the polynomial time trends or the cycle factor would suggest that the within- and across-cycle arousal rate time course differs between young and older participants, while the lack of such an interaction would suggest that the within- and across-cycle arousal time course is the same for both age groups. For the third aim, the modification with noise, the procedure was similar, evaluating main effects and significant two-way interactions to test whether the possible noise effect is uniform or non-uniform across the tested variables age, polynomial time trends, and cycle. In the case of non-significant interactions between age or noise and the polynomial CSD effects, we also tested the interaction between age or noise and CSD as a 10-level factor, to ensure that the lack of effect was not due to the specific parametrization of CSD.

Because of the similarity of the time course of arousal rates and that of SWS, which is more evident for the within- than the across-cycle time course, we added a separate analysis

that explored whether the variations in the percentage of SWS could partially or fully explain the variations of arousal rates within and across cycles. The use of a mediation analysis, the preferred statistical approach to address this type of question, is not yet implemented in the context of GLMM with a negative binomial distribution (see Supplement 2), so that we chose a very simplified approach to evaluate the effect of SWS. We compared the coefficients of determination (R^2) of the following five models: main effects (age, noise, polynomial time trends for CSD, and cycle) only (Model 1; M1), main effects and interactions (i. e. the final model (M2)), SWS only (M3), main effects and SWS (M4), and finally main effects, interactions, and SWS (M5). Additionally, we compared the significance of the main effects between M2 and M5.

All analyses were performed in R (R Core Team, 2018). All models were fitted using the *glmmTMB* library (v0.2.2.0; Brooks et al., 2017). We used the *car* package (v3.0-0; Fox & Weisberg, 2011) to evaluate significance of fixed effects using Wald chi-square tests. For post-hoc testing (marginal effects, interactions, and pairwise comparisons), we used the *emmeans* package (v1.2.3; Lenth, 2016) and adjusted p-values for multiple comparisons (Tukey method). Residuals for the GLMMs were simulated using the *DHARMa* package (v0.2.0; Hartig, 2018). R^2 was calculated using the *sjstats* package (v0.17.0; Lüdecke, 2018).

3 Results

3.1 Sleep variables

Sleep macro- and microstructure variables for the selected intervals of the first four sleep cycles as well as the effects of noise and age are depicted in Table 4.2. Older participants had higher percentages N1 and N2 sleep and lower percentage of SWS than young participants; latencies to N1, N2, and REM sleep as well as awakening rates from REM sleep did not differ between age groups. NREM EEG arousal rates were significantly higher in older than in young individuals ($\chi^2 = 14.79, P < 0.001$) and did not differ between noise types ($\chi^2 = 1.01, P = 0.602$). Differences between the selection of the first four sleep cycles and the all-night sleep period for all sleep variables are described elsewhere (see Supplement 1.1.1) and showed that the selected sleep period was characterised by better sleep with higher sleep efficiency, increased slow wave sleep, and lower arousal and awakening rates compared to the all-night sleep period.

Table 4.2: Sleep structure and continuity during selected intervals according to respective noise type and age group

Variable	Young Participants ($N = 26$)			Older Participants ($N = 16$)			Post-hoc test (age)		
	Noise-free 48 nights	Eventful 49 nights	Continuous 52 nights	Noise-free 25 nights	Eventful 25 nights	Continuous 30 nights			
TST (min)	359.2 (71.0)	372.4 (64.4)	373.8 (66.2)	335.3 (75.6)	355.7 (51.6)	323.5 (85.8)	*	young > older	
SE (%)	95.0 (3.0)	95.3 (3.2)	95.5 (2.8)	90.5 (4.4)	92.8 (3.6)	90.7 (8.5)	*	young > older	
Sleep latency N1 (min)	10.7 (8.5)	9.9 (8.2)	9.9 (7.0)	11.1 (6.1)	9.9 (6.2)	12.0 (11.3)			
Sleep latency N2 (min)	18.2 (10.3)	18.1 (10.3)	15.5 (8.2)	16.5 (7.7)	15.7 (6.9)	18.0 (12.1)			
SWS latency (min)	32.1 (14.9)	30.6 (10.8)	26.9 (8.2)	43.6 (29.9)	45.1 (38.3)	44.5 (24.4)	*	young < older	
REM latency (min)	76.3 (29.3)	64.9 (18.5)	67.0 (25.3)	74.7 (27.0)	69.2 (24.7)	64.5 (19.7)			#
Intra-sleep wake (% of TST)	2.0 (2.3)	1.8 (1.5)	1.6 (1.4)	6.2 (4.7)	4.9 (3.1)	4.9 (3.0)	*	young < older	
N1 sleep (% of TST)	11.8 (3.7)	11.6 (3.4)	11.3 (3.4)	17.3 (6.7)	16.1 (4.0)	17.5 (6.7)	*	young < older	
N2 sleep (% of TST)	45.8 (6.8)	45.0 (7.3)	45.4 (7.6)	48.6 (10.4)	53.5 (6.3)	50.9 (9.1)	*	young < older	
SWS (% of TST)	20.3 (7.6)	19.1 (6.9)	19.4 (7.9)	10.7 (11.5)	9.3 (6.3)	9.8 (9.1)	*	young > older	
REM (% of TST)	22.1 (5.7)	24.3 (5.7)	23.9 (5.1)	23.4 (5.3)	21.2 (4.4)	21.8 (5.8)			
EEG arousal rate (n/h TST)	10.0 (3.8)	10.6 (3.0)	10.6 (3.8)	17.6 (9.2)	16.2 (5.1)	18.2 (9.1)	*	young < older	
EEG arousal rate (n/h NREM)	9.4 (4.3)	10.0 (3.3)	9.9 (4.2)	16.3 (9.2)	14.9 (5.2)	17.1 (9.9)	*	young < older	
EEG arousal rate (n/h REM)	12.5 (5.7)	12.8 (6.0)	13.0 (6.4)	22.8 (15.5)	21.6 (9.8)	22.9 (13.8)	*	young < older	
Awakening rate (n/h TST)	1.3 (0.9)	1.3 (0.8)	1.2 (0.7)	2.0 (0.9)	1.9 (0.8)	1.8 (0.7)	*	young < older	
Awakening rate (n/h NREM)	1.3 (0.9)	1.5 (1.0)	1.3 (0.8)	2.2 (1.1)	2.2 (0.9)	2.1 (1.0)	*	young < older	
Awakening rate (n/h REM)	2.7 (2.5)	2.4 (1.9)	2.4 (2.0)	2.5 (2.0)	2.4 (1.6)	2.8 (2.3)			

Note. Means (Standard deviations). TST refers to total sleep time; SE: sleep efficiency = TST/TIB; TIB: time in bed; TIB here: lights off until the end of cycle 4. *: significant difference for post-hoc tests of the significant main effect for age. #: significant difference for post-hoc tests of the significant main effect for noise type: noise-free > continuous noise; (all $P < 0.05$, Tukey post-hoc).

3.2 Distribution of EEG arousal rates

Figure 4.2 displays the within- and across-cycle time course of number of EEG arousals (upper panels) and percentage time spent in SWS per CSD (lower panel). In the preliminary model, all main effects, i. e., the factors for age group, noise type, cycle, and CSD contributed significantly to the model (see Supplement for detailed results and intermediate steps). The 10-level-within cycle effect could be further reduced using fourth order polynomials, which included the following terms: a positive linear, a positive quadratic, a negative cubic, and a positive quartic component with the quadratic component being by far the most prominent. Five significant two-way interactions between factors were included in the model (see also Table 4.3), which are described in detail in the following. In addition, we included a first order autoregressive error structure (Likelihood-ratio test, $\chi^2 = 95.10, P < 0.001$) to account for the correlation of residuals within cycles across CSDs.

We observed a characteristic within-cycle distribution that was largely determined by a u-shaped pattern, as readily observable in the effects display of the predicted marginal means

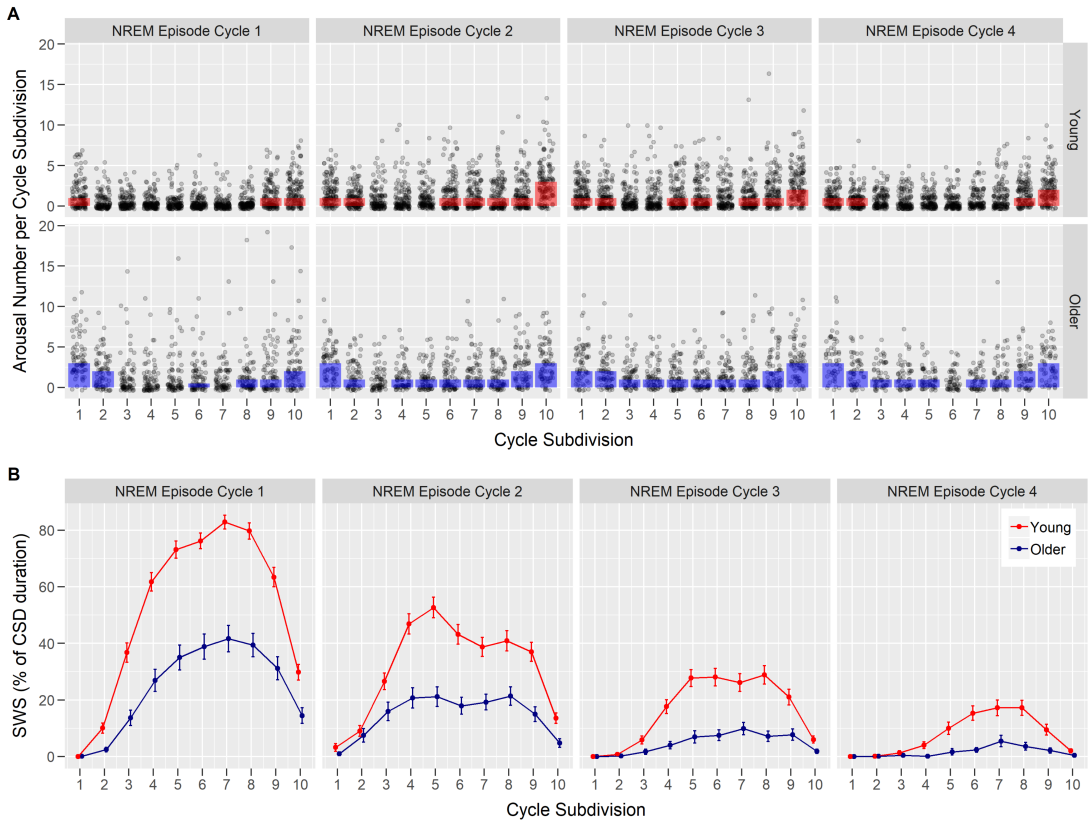

Figure 4.2: (A) Number of arousals (raw data) per cycle subdivision during the first four normalized NREM sleep cycles in young (in red, upper panel) and older (in blue, lower panel) individuals. Each dot depicts the number of EEG arousals during one night at the respective point in time; bars depict the median. **(B)** Slow wave sleep (SWS) as the average percentage of time spent in SWS per cycle subdivision (CSD) duration during the first four normalized sleep cycles in young (red) and older (blue) individuals. Error bars represent ± SEM. Cycle subdivision (CSD) is depicted with a standardized length of 6.9 min, the overall average CSD length.

in Figure 4.3A. However, the within-cycle time course was not independent of time of the night as indicated by the significant two-way interactions between cycle and the CSD linear, quadratic, and quartic trends, respectively. The *CSD linear trend*, describing the overall change in arousal rates from the beginning to the end of the cycle, was significantly different between cycle 1 and 2 and cycle 1 and 3 (Tukey post-hoc, $P < 0.007$ for all comparisons). The *CSD quadratic component* was responsible for the prominent u-shape of the distribution and the larger its coefficient, the narrower the u-shape. The quadratic coefficient was largest for the first cycle, smaller for the fourth cycle, and even smaller for the second and third cycle, reflected in the broader shapes in cycles 2 and 3. However, only the differences between cycle 1 and 2 and cycle 1 and 3 were statistically significant ($P < 0.001$ for all comparisons). The *third order polynomial trend* was not involved in any interaction and had a significant but minor effect compared to the other polynomial CSD effects. Its effect on the overall shape of the time course was to broaden the middle part of the cycle, changing the time course from a u-shape in the direction of a bathtub-shape. The effect of the *CSD quartic component* was to broaden the middle part of an already u-shaped time course by increasing the value in the middle (at 50 %) and decreasing the values in the middle of the first (25 %) and second half (75 %), thereby levelling the time course in this part of the cycle. The quartic coefficient was largest for cycle 2 and progressively smaller for cycles 3, 1, and 4. Post-hoc tests indicated that the quartic trend in cycle 4 was significantly smaller than all other cycles, and had an opposite sign compared to all other cycles ($P < 0.05$).

Table 4.3: Wald chi-square tests of the final model (M2)

Effect	χ^2	Df	P
Age	14.00	1	<0.001
Noise	6.76	2	0.034
Cycle	83.54	3	<0.001
CSD linear trend	19.40	1	<0.001
CSD quadratic trend	367.18	1	<0.001
CSD cubic trend	4.45	1	0.035
CSD quartic trend	20.02	1	<0.001
Age x Cycle	83.67	3	<0.001
Age x CSD linear trend	18.32	1	<0.001
Cycle x CSD linear trend	18.86	3	<0.001
Cycle x CSD quadratic trend	28.64	3	<0.001
Cycle x CSD quartic trend	19.73	3	<0.001

Note. CSD: cycle subdivision.

3.3 Modification with age

Because of the presence of significant interactions, we interpreted the significant main effect for age with caution; nevertheless, it is obvious that participants in the older age group had

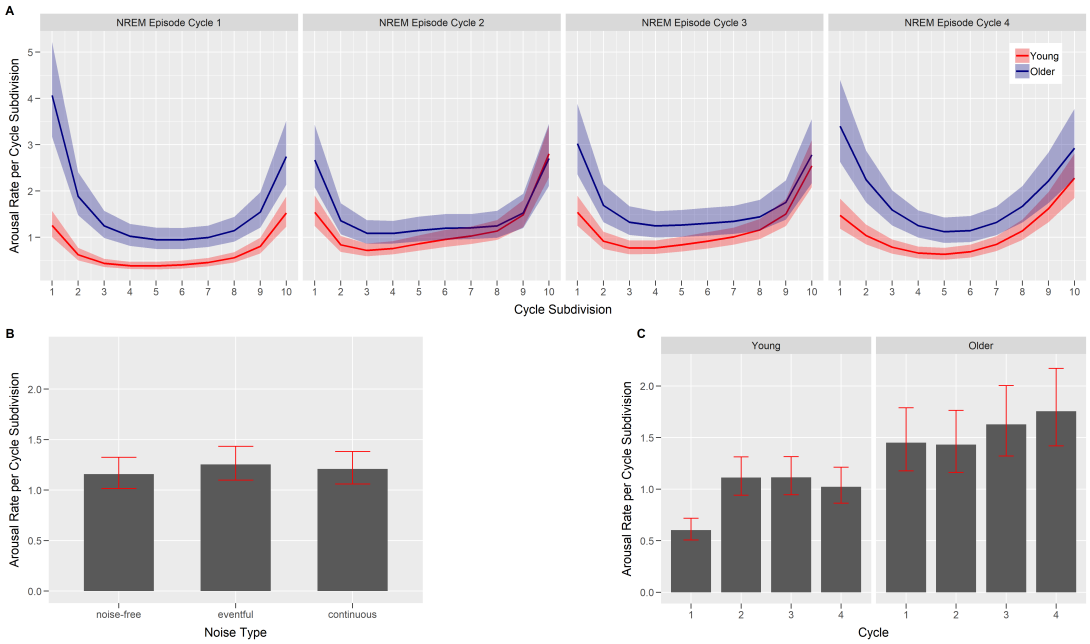

Figure 4.3: (A) Estimated marginal means for arousal rates based on the final model in young (red) and older (blue) individuals. **(B)** Estimated marginal means over the three different noise types. **(C)** Estimated marginal means over the NREM cycle for the two age groups. The EEG arousal rate displayed here is the number of arousals per cycle subdivision (CSD) with a standardized length of 6.9 min, the overall average CSD length. Mean ± 95 % confidence intervals.

a higher overall arousal rate than younger participants (Figure 4.3A and C). In addition, the significant interaction between cycle and age indicated that arousal rates were significantly lower during the first as compared to all other cycles in the young (Tukey post-hoc , $P < 0.001$ for all comparisons), while in the older, cycle 4 had significantly higher arousal rates than cycles 1 and 2 ($P < 0.005$ for all comparisons; Figure 4.3C). Post-hoc tests of the significant interaction between the CSD linear trend and age indicated that in the young age group, arousal rates at the end of the cycle were consistently higher than at the beginning of the cycle (CSD linear trend with a positive coefficient), while in the older age group, arousal rates tended to be higher at the beginning of the cycle compared to its end (CSD linear trend with a negative coefficient).

3.4 Modification with noise

Arousal rates were higher during the eventful (scenarios C and D) compared to the noise-free exposure scenario (Tukey post-hoc, $P = 0.03$; Figure 4.3B). All tested two-way interactions were non-significant, which included the interaction between noise and the age group ($\chi^2 = 1.46, P = 0.48$), noise and cycle ($\chi^2 = 12.10, P = 0.06$) and noise and the within cycle effects, both using polynomial time trends (CSD linear trend: $\chi^2 = 1.61, P = 0.45$; CSD quadratic trend: $\chi^2 = 0.30, P = 0.86$; CSD cubic trend: $\chi^2 = 3.19, P = 0.20$; CSD quartic trend: $\chi^2 = 1.32, P = 0.52$), or CSD treated as a factor ($\chi^2 = 19.86, P = 0.34$).

3.5 Effect of SWS

Table 4.4 gives the coefficients of determination for five different models: main effects only (M1), main effects and interactions (M2, our final model), SWS only (M3), main effects and SWS (M4), and main effects, interactions, and SWS (M5). Model 5 had the highest coefficient of determination among all tested models indicating that the inclusion of SWS further improved our final model. Comparing M2 and M3 revealed that our final model had a lower goodness of fit than the SWS only model indicating that SWS alone might be as good as the 12-term model (M2) in predicting the time course of EEG arousal rates. Nonetheless, the comparison between M3 and M4/M5 suggests that, independently of SWS, within- and across-cycle effects further improved the goodness of fit. Furthermore, in both comparisons (M1 vs. M2 and M4 vs. M5), the inclusion of significant two-way interactions in addition to the main effects improved the model fit. While both the noise condition and the interaction between cycle and CSD linear trend no longer contributed significantly to the model when SWS was included, all other predictors, main effects and interactions, still contributed significantly in both models (M2 and M5). More detailed results and a discussion of the shortcomings of our statistical approach are provided in the Supplement.

Table 4.4: Coefficients of determination (R^2) for the different tested models

	Model	R^2
M1	main effects only (age, noise, polynomial time trends, and cycle)	0.27
M2	main effects and interactions (final model)	0.35
M3	SWS only	0.38
M4	main effects and SWS	0.44
M5	main effects, interactions, and SWS	0.52

4 Discussion

The present analyses sought to examine the temporal distribution of EEG arousals both within and across sleep cycles and whether this distribution was modified by age and transportation noise exposure. The main results were: 1) arousal rates varied considerably within sleep cycles in a u-shaped or more bathtub-shaped course depending on the time of the night. 2) Older participants showed higher overall EEG arousal rates, being higher at the beginning than at the end of each NREM sleep episode in contrast to an opposite pattern in young participants. 3) EEG arousal rates increased during eventful noise exposure when compared to noise-free nights in both age groups across all NREM sleep episodes; although this was not consistent across analyses.

EEG arousal rates had a characteristic temporal distribution that was best described by a u-shaped curve with the highest number of arousals both at the beginning and end of a normalized NREM sleep episode. This characteristic distribution might be indicative of phases of decreased physiological sleep stability at the beginning and end of cycles. The results are in accordance with the distribution of CAP subtypes 2 and 3 which, per definition, share characteristics used for scoring EEG arousals (Halasz et al., 2004; Terzano & Parrino, 2000; Terzano et al., 2000, 2005). In general, the observed EEG arousal distribution is compatible with the typical NREM sleep architecture, which can be subdivided into three consecutive phases: initially, sleep stability is low and gradually EEG synchrony increases; next is a plateau phase of relative stability; and finally EEG synchrony rapidly declines towards REM sleep when sleep stability is again relatively low (Merica & Gaillard, 1986; Terzano & Parrino, 2000). The increase of EEG arousals preceding the onset of REM sleep in both age groups suggests a relationship with REM sleep and conditions that promote this state (Merica & Fortune, 1997; Terzano & Parrino, 2000; Terzano et al., 2005). We chose EEG arousal as a marker for ultradian variation of activation during sleep, but other activation indices also vary along the ultradian cycle. For the temporal distribution of body movements (Muzet, Naitoh, Townsend, & Johnson, 1972), heart rate dynamics (Cajochen et al., 1994), transient changes in EMG muscular tone (Brunner, Dijk, & Borbely, 1990) as well as EEG beta power fluctuations during sleep (Brunner et al., 1996) a time course similar to that of EEG arousals time has been described with activity peaks at the beginning and towards the end of NREM cycles. Finally, several heart rate variability indices also showed a marked u-shaped pattern within NREM cycles, though only in young but not in older individuals (Brandenberger et al., 2003).

Generally, EEG arousal rates increased across the night, but were only statistically different between the first and all other cycles in the young and between the fourth and all other cycles in the older. The across-cycle fluctuations are not in accordance with the literature where no variations were reported across cycles (Sforza et al., 2008) or time elapsed since sleep onset (De Gennaro et al., 2001) and might be explained by differences in methodological approaches and the EEG arousal definitions. De Gennaro et al. (2001) calculated arousal rates per hour of elapsed sleep time thereby not considering sleep cycles or any differences between NREM and REM sleep and Sforza et al. (2008) calculated arousal rates per sleep cycle, but pooled NREM and REM arousals. In addition, we adopted the standard 3-s minimum duration criterion (Berry et al., 2016), while Sforza et al. (2008) and De Gennaro et al. (2001) additionally included events with a duration between 1.5-3 s. On the other hand, this might only be a minor concern as apparently only 1.9 % of all arousal events were below 3 s in duration (Sforza et al., 2008).

The observed overall increase of EEG arousal rates in the older participants is consistent with the literature (Bonnet & Arand, 2007; Boselli et al., 1998; Terzano et al., 2002). Increased sleep fragmentation is a frequently reported age-related change of sleep architecture (Mander, Winer, & Walker, 2017) and might be due to the decreased ability to maintain consistent and stable sleep states with aging (Conte et al., 2014; Klerman et al., 2013). In the present study, age-related modifications of the EEG arousal time course were examined using interactions. There was a significant interaction with the CSD linear trend: while the linear trend was positive

in the young, indicating lower EEG arousal rates at the beginning compared to the end of a NREM episode, this coefficient was negative in the older. It might be speculated that increased EEG arousal rates at the beginning of a cycle reflect an impaired sleep deepening process when sleep states switch to NREM sleep, either from wakefulness during the sleep onset period or from REM sleep for subsequent sleep cycles. However, the other tested interactions with polynomial time trends lacked significance suggesting that the basic physiological texture of arousal distribution during sleep cycles is largely unaffected by age.

EEG arousal rates were increased during nights with eventful noise exposure compared to noise-free nights. The absence of significant interactions with noise exposure allows for the conclusion that EEG arousals during noise exposure nights occurred at similar points in time than during physiological conditions, therefore increasing the overall level but not changing the shape of the EEG arousal time course. This result was not consistent with results based on the all-night NREM EEG arousal rates (as depicted in Table 4.2) which were not affected by noise exposure likely due to methodological reasons. Occasionally, the REM episode of a cycle is interspersed with phases of NREM sleep–as long as this NREM sleep is shorter than a pre-defined time interval, per definition, this NREM sleep occurs during the REM episode (Feinberg & Floyd, 1979). For the all-night analysis, all EEG arousals occurring during NREM sleep were considered, while for the time course modelling only EEG arousals were considered that occurred during continuous NREM sleep episodes without any intervening REM sleep. Consequently, it is likely that the all-night analysis included more EEG arousals, namely those occurring during brief NREM intrusions during continuous episodes of REM sleep. Compared to the other effects in the final model, the noise effect was rather weak and the described small differences in considered NREM sleep might explain the significance of the noise factor in one but not the other analysis. During noise exposure nights, typically some of the EEG arousals are noise event-related (i. e., occur in temporal proximity to a noise event), while the other occur spontaneously (i. e., without an overt eliciting noise event). Indeed, many event-related EEG arousals replace spontaneous EEG arousals and only partly add to them (Basner et al., 2011). However, it is not possible to observe whether an observed arousal is a replacement or a true event-related arousal, which is why we decided to model the time course using all EEG arousals and not only a subset of event-related EEG arousals. Focussing on event-related EEG arousals only would also have limited analyses to two nights per individual as the other noise exposure nights included more continuous noise, which per design had few distinct events to relate EEG arousal to. Consequently, the strength of our experimental design is the inclusion of this two very different noise exposure situations and results suggest that only eventful noise had an effect on the microstructural architecture of NREM sleep when compared to noise-free conditions despite both eventful and continuous noise exposure nights having the same constant hourly $L_{Aeq,1h}$ of 45 dB.

Within cycles, the well-known evolution of SWS (Aeschbach & Borbély, 1993; Dijk et al., 1993) progresses inversely to the evolution of arousal rates so that we also tested whether the variations in the percentage of SWS could partially or fully explain the variations in arousal rates within and across sleep cycles. Regrettably, we could not use mediation analyses as these are not

yet implemented in the context of GLMM with a negative binomial distribution. We therefore compared coefficients of determination of different models as an approximation. However, computing coefficients of determination in the context of GLMMs is also challenging due to the treatment of the random effects as well as the underlying distribution, so that the respective results need to be interpreted with caution. Our results suggest that a considerable part of the observed effects could be mediated by SWS, but that even with SWS in the model, there were additional SWS-independent within- and across-cycle effects that contributed further to the model. Similarly, Terzano et al. (2005) reported that the time course of CAP subtypes A2 and A3, normalized in a similar way over the first five sleep cycles, was largely but not exclusively determined by SWA.

Our dependent variable, EEG arousal rate, contained a high number of zeros, a situation not uncommon in biology (Bohning, Dietz, Schlattmann, Mendonca, & Kirchner, 1999), which poses a particular challenge to any modeling. An excess number of zeros can have different reasons that significantly influence model choices (see Supplement 1.2.1). In the present analysis, we found that the distribution was consistent with a negative binomial distribution when all main effects were included in the model. Other model options, however, might also have been adequate. Of particular interest, are the so-called zero-altered models, which assume that there are actually two processes that produce the observed distribution with excess zeros. The first process determines whether or not there is any arousal, while the second process determines the number of arousals once the first process has overcome a critical threshold or hurdle. A tempting scenario is that the first process is represented by SWS while age, noise and the other effects represent the second process. The models presented in this paper can therefore be seen as a starting point and an intermediate representation rather than a final model. Another model choice that deserves discussion is the orthogonal polynomial time trends used to represent the within-cycle CSD effect. Our main concern was physiological interpretability of the effect which is not given when regarding CSD as a factor with 10 levels. Orthogonal polynomials are an alternative because they model a time course rather than single time points which improves interpretability, particularly when considering interactions, e. g. between group differences in the time course. However, this is only realistic for a limited number of polynomials. As detailed in the Supplement (1.2.2), a model with six polynomial trends fit the data as well as CSD as a factor but we decided to go with only four polynomial trends because we felt that six were no longer interpretable. Another option includes generalized additive mixed models (GAMM) that use flexible smoothing functions. However, choice of smoothing function and parameters would have added considerable complexity which in turns impedes interpretability. Nevertheless, this underlines that our presented model is but one of several possible and that there remain several promising avenues for future studies.

In conclusion, EEG arousal rates varied considerably within sleep cycles in a u-shaped or more bathtub-shaped course depending on the time of the night suggesting that both the beginning and the end of cycles are phases of reduced physiological sleep stability. Older participants had higher overall arousal rates and the shape of the arousal time course differed concerning the level between the beginning and the end of the cycle. Eventful transportation noise exposure

increased the overall level of EEG arousals but did not change the shape of the time course suggesting that eventful noise exposure leads to an unspecific increase of EEG arousals, which was embedded within the physiological structure of sleep stability during the night.

Limitations

Our analyses are based on a few limiting assumptions. The number of completed cycles can vary across nights both within and between individuals (Feinberg & Floyd, 1979; Merica & Gaillard, 1986). Here, we restricted the analysis to nights where the number of completed cycles was between three and five cycles assuming that fewer or more completed cycles represent outliers. Similarly, the duration of the NREM episode of a cycle was restricted to a duration between 33 and 116 min. Consequently, this procedure limits the generalisability of our results for nights with more, less, shorter, or longer cycles. Furthermore, we pooled data of individual nights with three, four, or five completed cycles assuming that within- and across-cycle effects on the arousal rate do not vary with the number of completed sleep cycles per night. To the best of our knowledge, differences in homeostatic regulation, spontaneous arousal rate, or arousal thresholds as a function of number of completed cycles have not yet been addressed in the literature, so that it remains open whether this assumption is valid.

Ultradian modulation of EEG arousals during sleep: effects of age and exposure to nighttime transportation noise - Supplement

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1 Distribution of arousals within and across NREM-REM cycles

The aim of these analyses were to investigate how arousal rates vary within and across NREM-REM cycles and whether this time course is affected by age, noise exposure, and ultimately SWS.

Here, we describe the model building steps including data exploration, model choices, operationalization of included factors, model building, and model diagnostics.

1.1 Data exploration, modelling strategies, and overall considerations

1.1.1 Selected vs. all-night sleep period

Our analyses only included the first three or four NREM-REM cycles and we therefore compared standard macro- and microstructure sleep variables between the selected sleep period with three/four cycles and the all-night sleep period with linear mixed models and the main effects for age group, noise type, and selected vs. all-night sleep period. Macro- and microstructure sleep parameters for the all-night sleep episode as well as the effects of the selection (first three/four sleep cycles vs. all-night) are displayed in Table 1 (those of the selected sleep period are displayed in Table 2 of the manuscript). Overall, the selected sleep period was characterised by better sleep with higher sleep efficiency, increased slow wave sleep, and lower arousal and awakening rates compared to the all-night sleep period.

Table 1: All-night standard macro- and microstructure sleep variables according to the respective noise type (continuous vs. eventful) and the age group (for a table with the respective variables for the selected intervals of 3 to 5 sleep cycles see main text)

	Young (N=26)			Older (N=16)			Post-hoc test
	Noise-free 48 nights	Eventful 49 nights	Continuous 52 nights	Noise-free 30 nights	Eventful 25 nights	Continuous 30 nights	
TST (min)	452.3 (17.9)	454.9 (16.1)	456.5 (16.2)	416.1 (33.5)	427.6 (30.0)	417.6 (42.5)	* 4 cyc < all-night
SE (%)	94.2 (3.7)	94.8 (3.4)	95.1 (3.4)	86.7 (7.0)	89.1 (6.3)	87.0 (8.9)	* 4 cyc > all-night
Sleep latency N1 (min)	10.7 (8.5)	9.9 (8.2)	9.9 (7.0)	11.1 (6.1)	9.9 (6.2)	12.0 (11.3)	-
Sleep latency N2 (min)	18.2 (10.3)	18.1 (10.3)	15.5 (8.2)	16.5 (7.7)	15.7 (6.9)	18.0 (12.1)	-
SWS latency (min)	32.1 (14.9)	30.6 (10.8)	26.9 (8.2)	43.6 (29.9)	45.1 (38.3)	44.5 (24.4)	-
REM latency (min)	76.3 (29.3)	64.9 (18.5)	67.0 (25.3)	74.7 (27.0)	69.2 (24.7)	64.5 (19.7)	-
Intra-sleep wake (% of TST)	3.1 (3.2)	3.2 (3.2)	2.6 (2.6)	10.5 (7.7)	9.2 (7.1)	12.5 (11.3)	* 4 cyc < all-night
N1 (% of TST)	13.0 (3.5)	12.7 (3.8)	12.2 (3.1)	19.3 (7.3)	18.4 (4.9)	19.7 (7.3)	* 4 cyc < all-night
N2 (% of TST)	47.6 (6.1)	46.8 (6.1)	47.6 (6.6)	50.7 (8.2)	53.3 (5.8)	52.5 (7.0)	* 4 cyc < all-night
SWS (% of TST)	17.5 (6.3)	16.9 (6.3)	17.3 (6.6)	8.3 (6.8)	8.3 (5.7)	7.6 (5.7)	* 4 cyc > all-night
REM (% of TST)	21.9 (4.3)	23.6 (4.9)	23.0 (4.7)	21.7 (5.4)	20.1 (4.5)	20.2 (4.9)	* 4 cyc > all-night
EEG Arousal rate (n/h TST)	10.1 (3.5)	10.7 (3.5)	10.8 (4.0)	18.3 (8.9)	17.4 (5.7)	18.9 (8.9)	* 4 cyc < all-night
EEG Arousal rate (n/h NREM)	9.4 (4.0)	10.2 (3.7)	10.2 (4.4)	17.3 (9.1)	16.4 (5.9)	18.4 (9.6)	* 4 cyc < all-night
EEG Arousal rate (n/h REM)	12.4 (5.8)	12.6 (5.6)	13.0 (6.2)	22.9 (14.3)	21.7 (10.3)	22.0 (13.3)	
Awakening rate (n/h TST)	1.5 (1.0)	1.6 (0.9)	1.5 (0.8)	2.2 (0.8)	2.5 (1.1)	2.6 (1.2)	* 4 cyc < all-night
Awakening rate (n/h NREM)	1.4 (1.1)	1.5 (1.0)	1.3 (0.8)	2.2 (0.9)	2.6 (1.3)	2.6 (1.4)	* 4 cyc < all-night
Awakening rate (n/h REM)	2.1 (1.9)	2.0 (1.8)	2.2 (2.0)	2.2 (1.9)	2.1 (1.7)	2.7 (2.2)	

Means ± standard deviations. TST refers to total sleep time; SE: sleep efficiency = TST/TIB; TIB: time in bed (480 min). *: significant difference according to respective post-hoc tests of the main effect of selection (first four sleep cycles vs. all-night; $P < 0.05$, Tukey).

1.1.2 Distribution of noise events across the night

In two of the six nights, the noise scenario included single, short noise events and we explored whether the distribution of these noise events was uniform across and within the NREM-REM cycles. As shown in Figure 1, noise events were evenly distributed across and within NREM-REM cycles (Cycle: χ^2 = 3.67, P = 0.300; CSD: χ^2 = 7.03, P = 0.634) supporting the choice to include all six nights in the analyses.

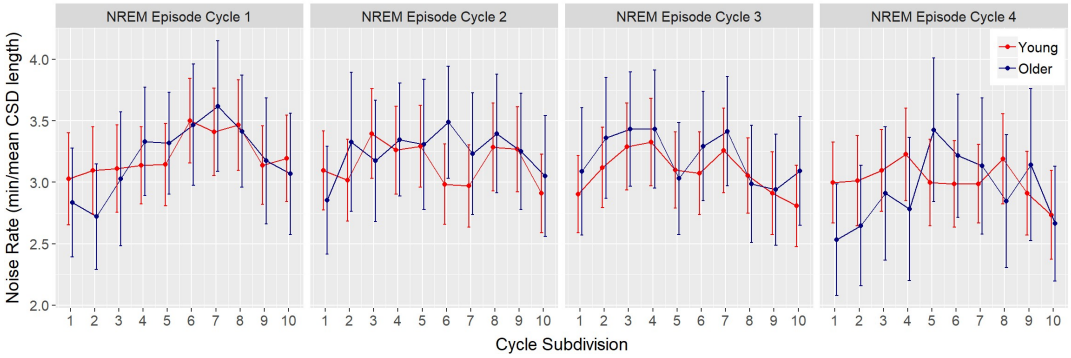

Figure 1: Distribution of noise rates (number of noise events per min/mean cycle subdivision (CSD) length) during the first four normalized NREM-REM cycles in young and older individuals. Error bars represent ± SEM.

1.1.3 Distribution of arousal rates and model choice

The dependent variable was originally expressed as the number of EEG arousals per average cycle subdivision (CSD) length in minutes to account for differences in the lengths of the CSDs (see below). However, as shown in Figure 2, the distribution of the arousal rates was highly skewed due to the absence of arousals in 45.38 % of the CSDs. Importantly, the distribution did not suggest any transformation to achieve normality.

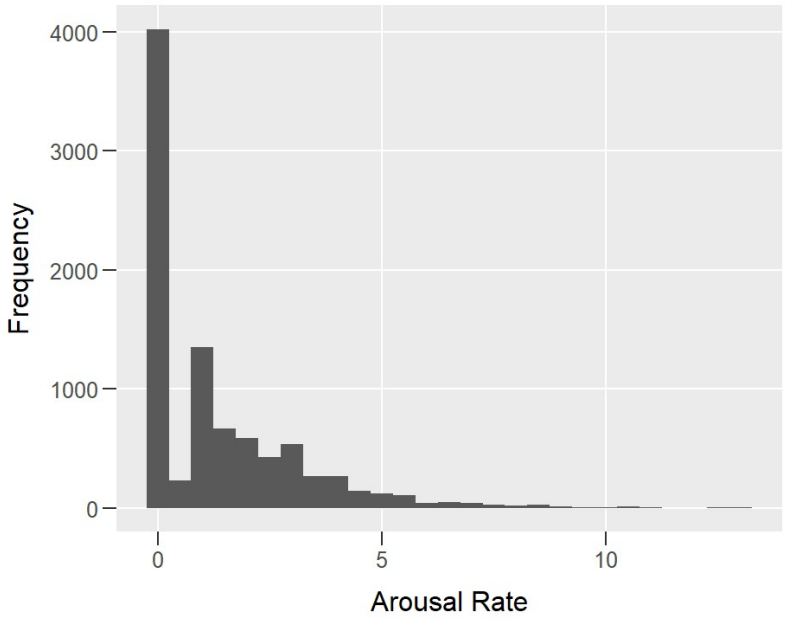

Figure 2: Distribution of arousal rate: number of arousals per average cycle subdivision length (min)

The distribution of the number of arousals (arousal frequency), however, was at least somewhat similar to the typical distribution of count variables such as a Poisson distribution (see Figure 3). Nevertheless, there is clearly an excess of zeros, a situation not uncommon in biology [1] and a goodness of fit test indicated that the data did not comply with a Poisson distribution (χ^2 = 84791, P < 0.001). The concern here is that when modelling this variable with, for example, a Poisson distribution, in all probability we will observe overdispersion, i.e. a residual variance that is larger than would be expected under the fitted model. If present, overdispersion is associated with p-values that are too small and confidence intervals that are too narrow [2].

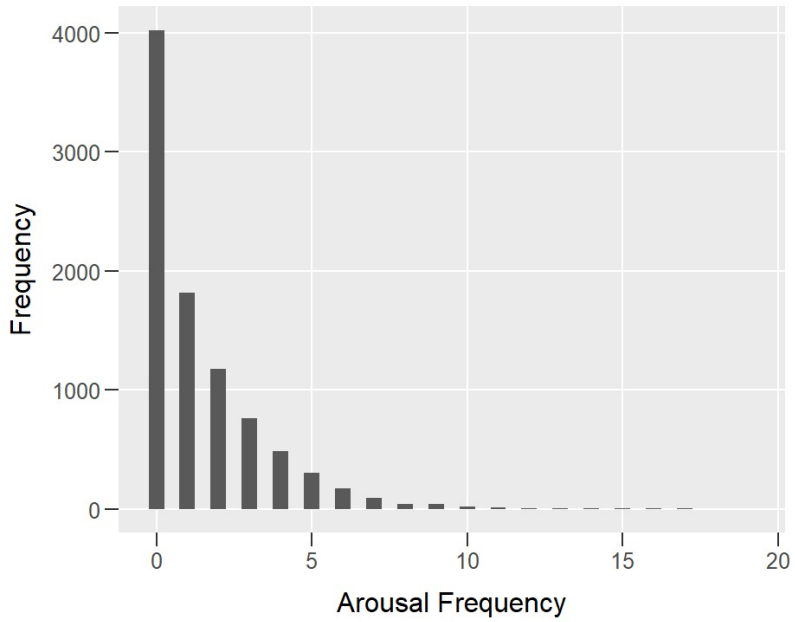

Figure 3: Distribution of arousal frequency (number of arousal during each cycle subdivision)

One possible approach in these situations, i.e. an overdispersion that is due to more zeros than would be expected, are zero-inflated models [3]. Their fundamental assumption is that the observed distribution is in fact a mixture of two separate distributions. One distribution is the one of the count variable (for example a Poisson or a negative binomial distribution) and describes the distribution of all non-zero values and as many zeros as are compatible with the underlying distribution. These zeros are called “true” zeros. The second distribution is that of all the remaining, excess zeros and these are assumed to be “false” zeros, i.e. false negatives due to observer, design or other errors.

Two possible sources of such false zeros in our study were cases where (i) there was no or very little sleep during a CSD or (ii) where the length of the CSD was too short. We addressed the first concern by excluding all CSDs with more than 50 % of wake, which occurred in 144 CSDs (1.68 %). Regarding the second concern, the length of the cycles, directly determining CSD length (10 % of cycle length), varied between 16 min and 189 min, and although approximately normally distributed included possibly outlying short and long cycles (Figure 4). Too long cycles are also potentially problematic since they could artificially increase the number of arousal.

We therefore decided to exclude single cycles with length below or above the lower/upper boxplot whiskers (i.e., the lower quartile - 1.5 times the interquartile range (IQR); the upper quartile + 1.5 times the IQR), a robust way to identify outliers [4]. The median NREM episode length was 70 min and 44 cycles (4.87 %) were excluded because they were shorter than 33 min (n = 8) or longer than 116 min (n = 36). 24 cycles were excluded in the young and 20 cycles in the older individuals. For the different noise exposure scenarios we excluded the following number of cycles: 19 during noise-free, 9 during eventful and 16 during continuous exposure nights. The minimum cycle length was therefore 33 min and we also excluded those CSDs that contained wake and where the duration of sleep was less than 3 min (n = 24 CSDs, 0.29 %).

The final data set included 8382 CSDs in 855 cycles from 234 nights in 42 participants.

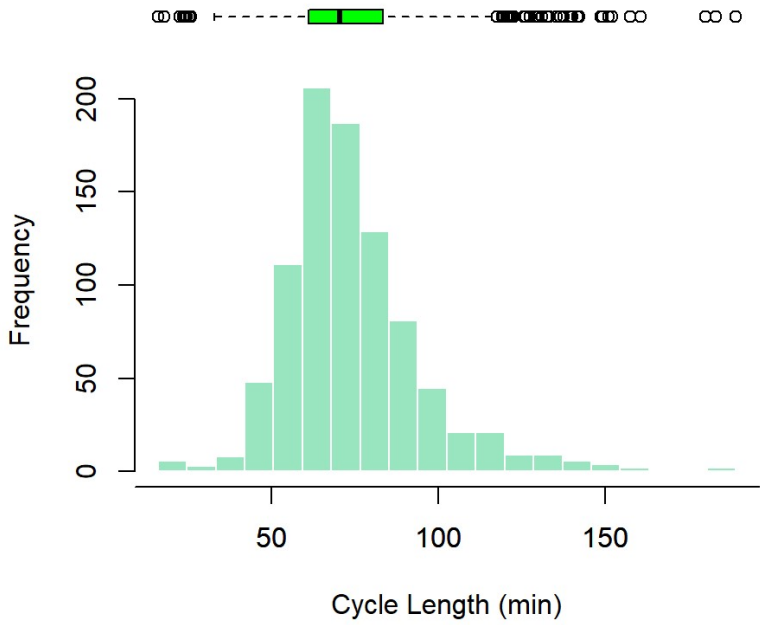

Figure 4: Distribution of cycle length

Even after eliminating CSDs that could have produced false zeros, the distribution of arousal frequency in CSDs still contained an excess of zeros and did not comply with a Poisson distribution (χ^2 = 75261, P < 0.001).

We therefore considered several possible strategies. Because each participant contributed multiple data points, all models are variants of hierarchical or mixed models with a random intercept for each participant. The dependent or response variable is the arousal rate, but instead of using the actual rates (number per hour), we modelled the arousal frequency (number of arousals) and included an offset (the logarithm of CSD length) in the model. In the case of a Poisson, negative binomial distribution, or geometric distribution this is mathematically equivalent to modelling the rates but has the advantage that the fitted values are always positive, the confidence intervals of the fitted values do not contain negative values, and heterogeneity can be accommodated by choosing from a range of different distributions (for details see [3]). The overall model class were therefore generalized mixed models (GLMM). The explanatory or independent variables were age group (young vs. older), noise type (noise-free vs. eventful noise vs. continuous noise), cycle (1 to 4), and CSD (1 to 10) and we considered their main effects as well as all two-way interactions.

As detailed below, we explored several basic model choices with the aim to find a model where the error terms or residuals follow a uniform or flat distribution, the GLMM equivalent to a normal distribution in linear mixed models. Standardized quantile residuals were generated with a simulation-based approach (n = 250) implemented in the R package DHARMa [5], which overcomes many of the difficulties when evaluating GLMM residuals. In short, new data sets (n = 250) are simulated from the fitted model, thus generating for each observation in the original data set a distribution of simulated observations. The residual is then defined as the value of the empirical density function (of the simulated observations) at the value of the observation, e.g. 0.2 means that 20 % of the simulated values are smaller than the observed value, 0.5 means that half

are smaller, and 0.9 occurs when 90 % of the simulated observations are smaller. If the model is correctly specified, all values of the simulated distribution will appear with equal probability and we would therefore expect the distribution of the residuals to be flat. This can be formally tested, for example by using the Kolmogorov-Smirnov (KS) test for overall uniformity of the residuals as implemented in DHARMa.

1.2 Model building

As detailed below, we started with a simple model with only the main effects, the offset, and a random subject effect and explored residual variances with respect to different discrete distributions. The main effects and only factors considered were age group (young vs. older), noise type (noise-free vs. eventful noise vs. continuous noise), cycle (1 to 4), and CSD (1 to 10). Next, we evaluated orthogonal polynomial time trends regarding their ability to represent the 10-level-within cycle effect with fewer parameters. After this, we explored all possible two-way interactions and added them to the model. In the resulting model with all fixed effects specified, we first addressed possible collinearity between the fixed effects, as well as residual variance heterogeneity and time related error structures. In a final step, we explored whether the resulting model could be simplified.

At this point, variations in arousal rates across the night had been modelled as a function of NREM-REM cycle and position within NREM-REM cycle. Since the time course of arousal rates was strikingly reciprocal to that of slow wave sleep (SWS), we added a separate analysis, that explored whether the variations in the percentage of SWS could partially or fully explain the variations in arousal rates across and within NREM-REM cycles.

1.2.1 Main effects and choice of distribution

Our simplest model contained the main effects age group, noise type, across- and within-cycle effects as well as the offset and a random subject effect (Table 2). All four effects were found to have a significant effect on arousal rate ($P < 0.05$, Wald chi-square tests).

Table 2: Wald chi-square tests of the baseline model

	χ^2	Df	P
Age	12.670	1	<0.001
Noise	7.210	2	0.027
Cycle	100.510	3	<0.001
CSD	1078.006	9	<0.001

We fitted these effects before evaluating the residual structure, because a common cause of overdispersion is a misspecified model, often due to important factors missing from the model. Subsequently, we considered three discrete distributions where the variances equal the mean (Poisson) or variances increase linearly (negative binomial) or quadratic (geometric) with the mean. Both the quantile-quantile (QQ) plot of the residuals against a uniform distribution and the KS test supported the choice of a negative binomial distribution (Figure 5). Consistent with this, the test for zero-inflation indicated no concerns with a negative binomial distribution (observed/simulated ratio 1.015, $P = 0.656$, Figure 6).

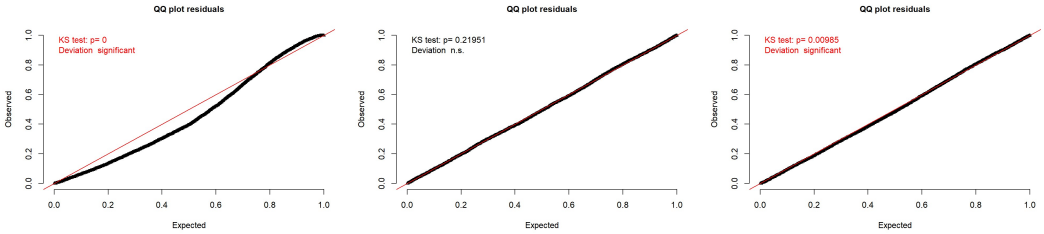

Figure 5: Quantile-quantile plots of the simulated residuals against a uniform distribution and Kolmogorov-Smirnov (KS) tests. Results for models fitted with a Poisson (left), a negative binomial (middle), or a geometric (right) distribution.

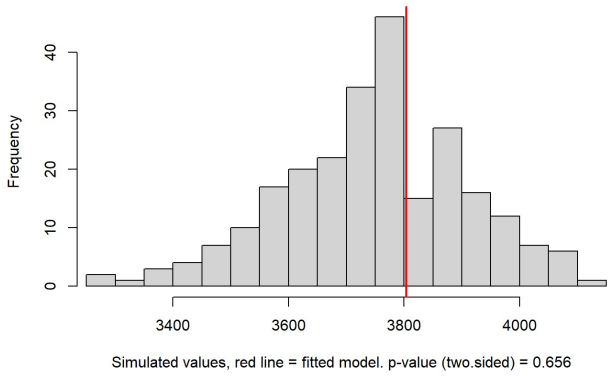

Figure 6: Distribution of expected zeros and observed zeros (in red) for detection of zero inflation in the model fitted with a negative binomial distribution

1.2.2 Modelling the within-cycle effect

In the above model, CSD had been introduced as a factor with 10 levels. Visual inspection of the effects display suggested that arousal rates followed a roughly u-shaped function across the cycle (Figure 7).

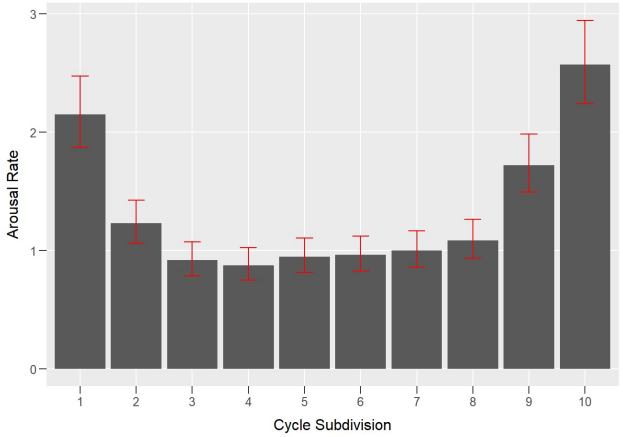

Figure 7: Cycle subdivision effect: estimated marginal means based on a model including cycle subdivision as a 10-level factor. Error bars represent 95 % confidence intervals.

We therefore explored orthogonal polynomials up to the 6th level by fitting first a model with all six levels and then dropping one level at a time. While we were not actually considering to continue with a model with a 6th order polynomial, we fitted this model for comparison. Likelihood ratio tests were used to compare models to each other and to the basic model with CSD as a factor.

We found that a 6th order polynomial model performed as good as the model with CSD as a factor (LRT: p=0.731) and better than models with a 5th, 4th, or 3rd order polynomial effect (Table 3).

Table 3: Comparisons between different models that represented cycle subdivisions as a 10-level factor or with a 6th (P6), 5th (P5), 4th (P4), or 3rd (P3) order polynomial. Test statistics derived from Likelihood Ratio tests.

	10-level factor	**p6**	**p5**	**p4**
p6	χ^2 =1.29, p=0.731			
p5	χ^2 =10.51, p=0.033	χ^2 =9.22, p=0.002		
p4	χ^2 =14.70, p=0.012	χ^2 =13.41, p=0.001	χ^2 =4.19, p=0.041	
p3	χ^2 =41.35, p<0.001	χ^2 =40.06, p<0.001	χ^2 =30.84, p<0.001	χ^2 =26.66, p<0.001

Because we judged a model with 6 polynomial trends too complex to interpret, and taking into consideration that - although significant - the differences between a baseline model and the 4th or 5th order models were - judged by the respective χ^2 statistic - moderate, we inspected the fitted values of the different models to better evaluate their differences. In Figure 8, the within-cycle effect is shown for the models with 3rd to 6th order polynomial effects.

These plots suggested that the characteristic time course of the arousal rates is preserved in models with 4 or more polynomials, while three polynomials are over-smoothing the time trend. At this moment we considered whether to go ahead with a 4th polynomial trend, which is still interpretable and preserved the time course of the arousal rate, or switch to a generalized additive mixed models (GAMM) with smoothing splines for the CSD effect. We decided to go ahead with the polynomial model, but kept GAMM as an option should model evaluation reveal any problems.

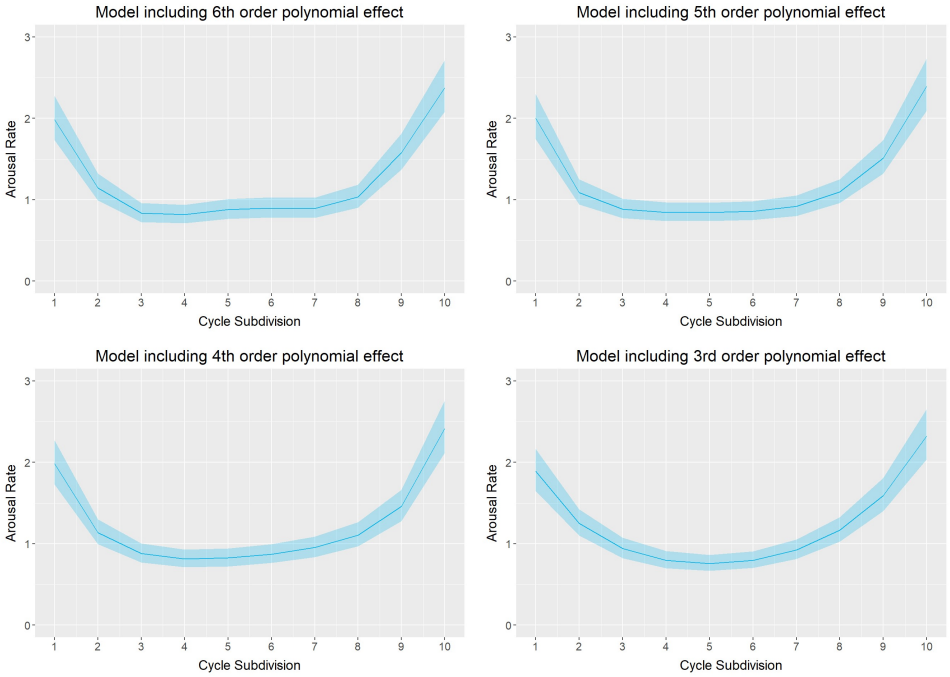

Figure 8: Cycle subdivision effect: estimated marginal means based on models including different order polynomials. Bands represent 95 % confidence intervals

1.2.3 Interaction between age, noise, across- and within-cycle effects

In the next step, we systematically evaluated all two-way interactions between age group, noise type, cycle and the linear, quadratic, cubic, and quartic trend for the CSD. These interactions test effects such as that the time course of arousal rates is different between young and older participants or that noise is associated with a different within-cycle distribution of arousal rates.

Adding each interaction individually to the model, showed significant interactions of age with cycle (LRT, χ^2 = 82.43, P < 0.001) and the linear (χ^2 = 63.96, P < 0.001) and cubic CSD polynomial trend (χ^2 = 15.52, P < 0.001) as well as an interaction between cycles and the linear, quadratic, and quartic CSD trends (linear: χ^2 = 20.33, quadratic: χ^2 = 24.14, quartic: χ^2 = 17. 52, all P < 0.001). When adding all significant interactions to the model, the interaction of age with the CSD cubic trend did no longer reach significance and was removed.

The intermediate model is shown in Table 4.

Table 4: Wald chi-square tests of the intermediate model

	χ^2	Df	P
Intercept	729.023	1	<0.001
Age	40.184	1	<0.001
Noise	7.141	2	0.0281
Cycle	166.289	3	<0.001
CSD linear trend	10.223	1	0.0014
CSD quadratic trend	289.719	1	<0.001
CSD cubic trend	6.420	1	0.0113
CSD quartic trend	6.108	1	0.0135
Age x Cycle	81.368	3	<0.001
Age x CSD linear trend	60.273	1	<0.001
Cycle x CSD linear trend	18.480	3	<0.001
Cycle x CSD quadratic trend	28.611	3	<0.001
Cycle x CSD quartic trend	20.562	3	<0.001

1.2.4 Model diagnostics

Model evaluation included three steps. First, we tested for collinearity of the predictors, using an adapted version of the variance inflation factor (VIF) for GLMM ([6] and below). The cutoff-value for the variance inflation factor (VIF) is a matter of debate: values above 10 definitely suggest the need to reconsider the model, but values as low as 5 or 2.5 might also prompt some investigation. As listed below, three of the four VIFs of the CSD polynomial trends had values between 5 and 6.

Table 5: Variance inflation factors for the predictors in the final model including the unstructured covariance structure

	VIF
Age_older	1.142
Noise_eventful	1.337
Noise_continuous	1.338
Cycle_2	3.684
Cycle_3	3.727
Cycle_4	3.388
CSD linear trend	6.006
CSD quadratic trend	5.391
CSD cubic trend	1.133
CSD quartic trend	5.351
Age_older x Cycle_2	2.947
Age_older x Cycle_3	2.997
Age_Older x Cycle_4	2.713
Age_older x CSD linear trend	1.855
Cycle_2 x CSD linear trend	2.303
Cycle_3 x CSD linear trend	2.337
Cycle_4 x CSD linear trend	2.045
Cycle_2 x CSD quadratic trend	2.810
Cycle_3 x CSD quadratic trend	2.821
Cycle_4 x CSD quadratic trend	2.396
Cycle_2 x CSD quartic trend	2.568
Cycle_3 x CSD quartic trend	2.629
Cycle_4 x CSD quartic trend	2.296

Although the polynomial main effects had the elevated VIF values, VIF values for the baseline model without interactions were all well within limits, arguing that the interaction involving this effects rather than the main effects were responsible. Indeed, inspection of the estimated correlation of the fixed effects showed that the largest correlations were those between the CSD trends and their interaction with cycle. These moderately increased VIF values for effects, which because of their involvement in interaction will not be interpreted, were only mildly concerning but we explored nevertheless whether we could simplify the model by collapsing across categories of cycle. For this to be a possibility, we would have to identify factor levels that did not differ, neither as a main effect nor in any of the interactions with age and the polynomial trends. This, however, was not the case and since we had not yet addressed the residual covariance structure, we took no further action but planned to re-evaluate VIF values at a later time.

Next, we evaluated the residuals of the resulting model. Besides again testing whether residuals were compatible with a uniform distribution (Figure 9), we explored whether there was any heterogeneity of residuals with respect to the model covariates (Figure 10). None of the results gave any reason for concerns.

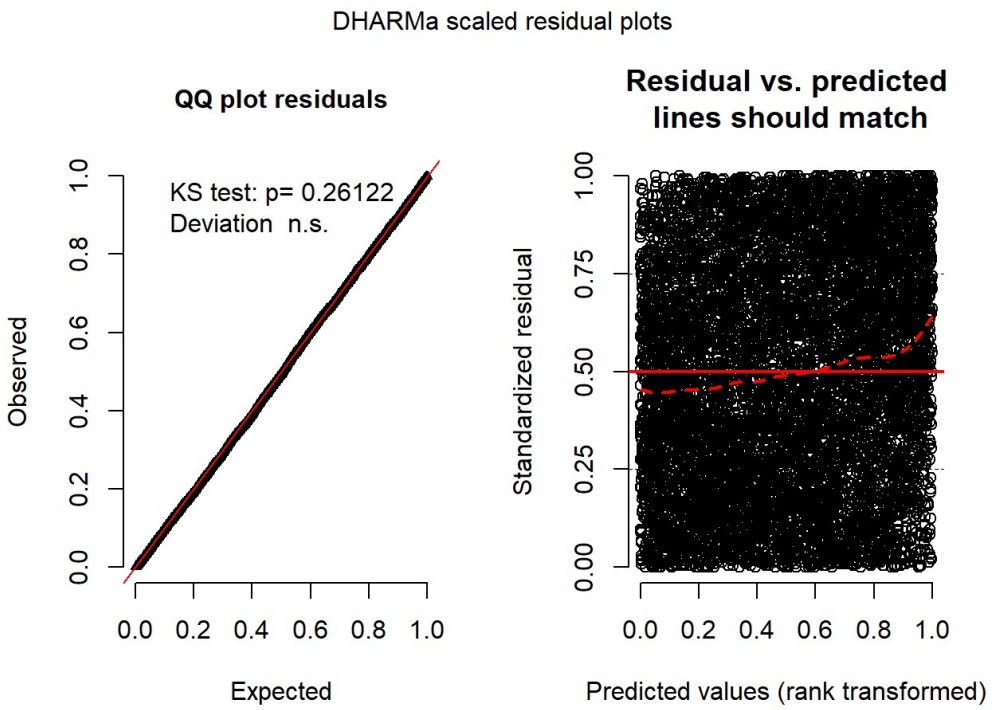

Figure 9: Expected against observed residuals (left panel) and simulated residuals against fitted values (right panel)

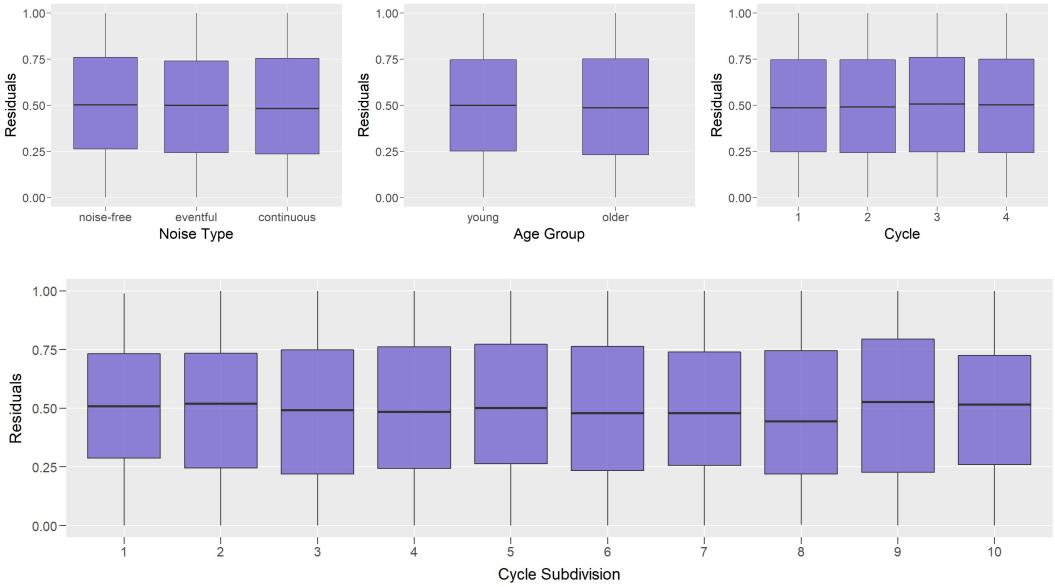

Figure 10: Simulated residuals plotted against model covariates to evaluate heterogeneity of residuals

Finally, we evaluated the possibility that residuals were correlated within cycle across CSDs. The Durbin-Watson test indicated significant autocorrelation of residuals (DW = 1.86, P < 0.001) and we therefore added a first order autoregressive (AR(1)) covariance structure to the model. The underlying assumption is that correlations are highest for adjacent points of time and decrease as a function of the time lag between observations. The model with the AR(1) covariance structure fitted the data significantly better (LRT, χ^2 = 95.10, P < 0.001) and the estimated off-diagonal correlation, i.e. the correlation between the arousal rates of two adjacent CSDs, was 0.77.

Since we changed the covariance structure of the model, we re-evaluated the fixed effects. All fixed effects remained substantially unchanged, but the variance inflation factors were significantly reduced with all VIF values within an unproblematic range (all VIF < 4.1). There was also no indication that we could simplify the model further.

1.3 Results

The final model is described in Table 6 and the effects are displayed in Figure 11. The arousal rate displayed here is the number of arousals per CSD with a standardized length of 6.9 minutes, the overall mean CSD length. While the noise-free and the continuous exposure condition did not differ, arousal rates were higher during the eventful noise exposure compared to the noise-free condition (Tukey post-hoc test, P = 0.026).

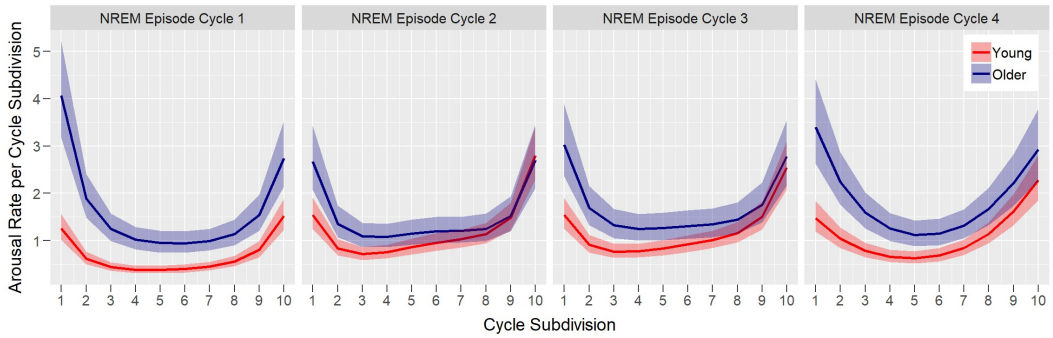

Figure 11: Estimated marginal means based on the final model. Bands represent 95 % confidence intervals.

Several of the model's effects are readily observable in the effects display of the predicted marginal means with their 95 % confidence interval (Figure 11). For one, it is obvious that participants in the older age group had a higher arousal rate than younger participants, independent of and additive to the interaction between age group and cycle and polynomial trends. Next, the linear effect describes the overall change in arousal rate from the beginning to the end of the cycle. In the young age group, arousal rates at the end of the cycle were consistently higher than at the beginning of the cycle, while in the older age group, arousal rates tended to be larger at the beginning of the cycle compared to its end. The correspondence of this interaction in the model (see Table 6) was a positive linear coefficient for the young (0.29) and a negative linear coefficient in the older group (-0.30). The significant interaction between cycle and age indicated further that arousal rates were significantly lower during the first as compared to all other cycles in the young (P < 0.001 for all comparisons), while in the older, cycle 4 had significantly higher arousal rates than cycles 1 and 2 (P < 0.005 for all comparisons).

The within-cycle trend was modelled by up to 4th order polynomials and of these the quadratic trend was by far the most dominant. The quadratic trend is responsible for the prominent u-shape of the distribution. The model coefficient for the quadratic trend determines the narrow or broad the u-shape is, and the larger the coefficient, the narrower the u-shape. The sign of the coefficient determines whether the course is u-shaped (positive coefficient) or has an inverted u-shape (negative coefficient). In our model, the quadratic coefficient was largest for the first cycle (1.45), smaller for the 4th cycle (1.18), and even smaller for the second (0.95) and third cycle (0.94), reflected in the broader shapes in cycles 2 and 3. However, only the differences between cycle 1 and cycles 2 and 3 were statistically significant ($P < 0.001$ for all comparisons).

The 3rd order polynomial trend was not involved in any interaction and had a significant but comparatively minor effect. The form of a 3rd order polynomial is that of one full sinus wave cycle starting at $-\pi$, i.e. a u-shape in the first half and an inverted u-shape in the second half of the cycle. It's effect on the overall shape of the time course was to broaden the middle part of the cycle, changing the time course from a u-shape in the direction of a bathtub-shape.

A 4th order polynomial trend has the form of the letter "W" and its effect on the overall shape can be best seen in cycle 2. The larger the quartic coefficient, the more pronounced the height of the W-shape. It's effect on an already u-shaped time course is to broaden the middle part by increasing the value in the middle (at 50 %) and decreasing the values in the middle of the first (25 %) and second half (75 %), thereby leveling the time course in this part of the cycle. The 4th order coefficient was largest for cycle 2 (0.39), and progressively smaller for cycles 3 (0.26), 1 (0.22), and 4 (-0.08). Post-hoc tests indicated that the quartic trend in cycle 4 was significantly smaller, and indeed had an opposite sign, than all other cycles ($P < 0.05$).

In summary, arousal rates varied considerably within NREM-REM cycles in a u-shaped or more bathtub-shaped course depending on the time of the night. Older participants did not only have higher overall arousal rates, but also a more pronounced shape with arousal rates being higher at the beginning than at the end of a cycle, with the opposite pattern in young participants.

Table 6: Wald chi-square tests of the final model (M2)

	χ^2	Df	P
Age	13.998	1	<0.001
Noise	6.756	2	0.034
Cycle	83.536	3	<0.001
CSD linear trend	19.400	1	<0.001
CSD quadratic trend	367.181	1	<0.001
CSD cubic trend	4.446	1	0.035
CSD quartic trend	20.021	1	<0.001
Age x Cycle	83.667	3	<0.001
Age x CSD linear trend	18.316	1	<0.001
Cycle x CSD linear trend	18.855	3	<0.001
Cycle x CSD quadratic trend	28.639	3	<0.001
Cycle x CSD quartic trend	19.728	3	<0.001

2 The role of SWS

The above described time course of arousal rates mirrors in some way that of SWS and indeed the time course of SWS was strikingly reciprocal to that of the arousal rates (Figure 12). Therefore, in a last step, we explored whether the variations in the percentage of SWS could partially or fully explain the variations in arousal rates across and within cycles.

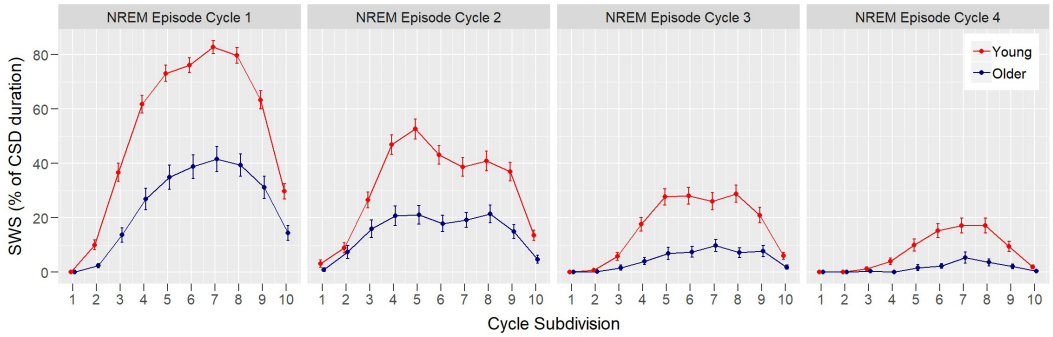

Figure 12: Slow wave sleep (SWS) in % per cycle subdivision (CSD) duration during the first four normalized NREM-REM cycles in young and older individuals. Error bars represent ± SEM.

Usually, mediation analysis is the preferred statistical method to test the influence of an additional variable on the relation between an independent and a dependent variable. Testing for mediation, typically comprises the evaluation of four steps in the classical mediation approach: (i) testing the direct effect (the one to be mediated), testing the indirect effect including (ii) the effect of the independent variable on the mediator and (iii) the effect of the mediator on the dependent variable, and (iv) evaluation of the mediation: an effect is called complete when the direct effect is no longer significant in a model now including the mediator; it is partially mediated when the magnitude of the direct effect is lower in a model including the mediator as compared to a model without the mediator [7]. Regrettably, we were not able to use mediation analysis in our case for several reasons. One reason was that we did not only use a single but multiple independent variables to model EEG arousal rates. Advanced statistical methods allowing for multiple independent variables exist, but, to the best our knowledge, are not yet implemented in an accessible form. In addition, their application in clustered, repeated measures data with only moderate sample size is highly problematic [7]. Finally, the distribution of the SWS, i.e. the percentage of SWS per cycle subdivision, was bimodal with peaks at 0 (in 60 % of all CSDs) and 100 percent (11 %) and had an uniform distribution between these two extremes. Since one of the steps in mediation analysis would have included a model with SWS as the dependent variable, this distribution would pose considerable, perhaps insurmountable, challenges to model building and interpretation.

We chose the following approach to at least approximate the evaluation of a mediating effect of SWS. First, we compared the coefficients of determination, R^2 , between five models: main effects (age, noise, cycle, and polynomial time trends) only (M1), main effects and interactions (i.e. the final model (M2)), SWS only (M3), main effects and SWS (M4), and main effects, interactions, and SWS (M5). Second, we compared the significance of each fixed effect between M2 (final model) and M5 (final model and SWS).

It must be noted that the estimation of R^2 is challenging in the context of GLMM with some concerns regarding the treatment of the random effects as well as the sampling variation of the underlying distribution, i.e. the negative binomial distribution in our case. Conditional R^2 was

calculated according to the recommendations of Nakagawa et al. [8] as implemented in the R package sjstats [9]. The results are described in Table 7, but for the reasons discussed need to be interpreted with caution.

Table 7: Conditional R^2 for the different models

	Model	R^2
M1	main effects only (age, noise, polynomial time trends, and cycle)	0.27
M2	main effects and interactions (final model)	0.35
M3	SWS only	0.38
M4	main effects and SWS	0.44
M5	main effects, interactions, and SWS	0.52

Comparing R^2 for the different models showed that model 5 had the highest goodness of fit among all tested models indicating that the inclusion of SWS considerably improved our final model. Comparing M2 and M3 showed that our final model had a worse fit than the SWS-only model indicating that SWS might be as efficient as a 12-term model (M2) in predicting the time course of EEG arousal rates. Nonetheless, the comparison between M3 and M4/M5 suggested that the effect was not solely due to SWS and that across and within cycle effects were important model predictors improving the goodness of fit further when included. Furthermore, in both comparisons (M1 vs. M2 and M4 vs. M5), the inclusion of significant two-way interactions in addition to the main effects improved model fit.

When comparing the significance of the fixed effects between the two models (Table 8), it seemed that the inclusion of SWS reduced the complexity of the model as both the noise condition and the interaction between cycle and CSD linear trend did no longer contribute significantly to the model when SWS was additionally included. We have no other explanation for the difference regarding the noise effect as that its contribution in the final model was already weak. The interaction effect was mainly driven by a significantly different first cycle and it is to be assumed that this cycle effect was better covered by SWS. All other predictors, main effects and interactions, contributed significantly in both models.

Table 8: Comparison of fixed effects between the final model (M2) and the final model plus SWS (M5)

	χ^2 (M2)	Df (M2)	P (M2)	χ^2 (M5)	Df (M5)	P (M5)
Age	13.998	1	<0.001	6.785	1	0.0092
Noise	6.756	2	0.034	4.935	2	0.0848
Cycle	83.536	3	<0.001	34.666	3	<0.001
CSD linear trend	19.400	1	<0.001	53.971	1	<0.001
CSD quadratic trend	367.181	1	<0.001	120.417	1	<0.001
CSD cubic trend	4.446	1	0.035	22.656	1	<0.001
CSD quartic trend	20.021	1	<0.001	22.043	1	<0.001
Percentage SWS	NA		NA	804.273	1	<0.001
Age x Cycle	83.667	3	<0.001	57.999	3	<0.001
Age x CSD linear trend	18.316	1	<0.001	24.125	1	<0.001
Cycle x CSD linear trend	18.855	3	<0.001	5.720	3	0.1260
Cycle x CSD quadratic trend	28.639	3	<0.001	37.425	3	<0.001
Cycle x CSD quartic trend	19.728	3	<0.001	23.662	3	<0.001

To conclude, it seems likely that the observed effects on the EEG arousal time course are mediated by SWS, that this mediation is partial and that both within- and across cycle time contributes in an SWS-independent manner to the prediction of the EEG arousal time course. At this moment, however, this is mere speculation as these mechanisms need to be investigated with more adequate statistical approaches.

3 R environment and packages

- Version: R version 3.5.1 (2018-07-02)
- OS: Windows 10 x64
- Packages: abind 1.4-5 [CRAN (R 3.5.0)], assertthat 0.2.0 [CRAN (R 3.5.1)], backports 1.1.2 [CRAN (R 3.5.0)], bayesplot 1.5.0 [CRAN (R 3.5.1)], broom 0.5.0 [CRAN (R 3.5.1)], callr 2.0.4 [CRAN (R 3.5.1)], car 3.0-2 [CRAN (R 3.5.1)], carData 3.0-1 [CRAN (R 3.5.0)], cellranger 1.1.0 [CRAN (R 3.5.1)], checkmate 1.8.5 [CRAN (R 3.5.1)], cli 1.1.0 [CRAN (R 3.5.3)], coda 0.19-1 [CRAN (R 3.5.1)], codetools 0.2-15 [CRAN (R 3.5.1)], coin 1.2-2 [CRAN (R 3.5.1)], colorspace 1.3-2 [CRAN (R 3.5.1)], crayon 1.3.4 [CRAN (R 3.5.1)], curl 3.2 [CRAN (R 3.5.1)], data.table 1.11.4 [CRAN (R 3.5.1)], desc 1.2.0 [CRAN (R 3.5.3)], devtools 2.0.1 [CRAN (R 3.5.3)], DHARMa 0.2.0 [CRAN (R 3.5.1)], digest 0.6.15 [CRAN (R 3.5.1)], dplyr 0.8.0.1 [CRAN (R 3.5.3)], effects 4.0-2 [CRAN (R 3.5.1)], emmeans 1.2.3 [CRAN (R 3.5.1)], estimability 1.3 [CRAN (R 3.5.0)], evaluate 0.11 [CRAN (R 3.5.1)], forcats 0.3.0 [CRAN (R 3.5.1)], foreach 1.4.4 [CRAN (R 3.5.1)], foreign 0.8-70 [CRAN (R 3.5.1)], fs 1.2.7 [CRAN (R 3.5.3)], ggplot2 3.0.0 [CRAN (R 3.5.1)], ggpubr 0.2 [CRAN (R 3.5.3)], ggridges 0.5.0 [CRAN (R 3.5.1)], glmmTMB 0.2.2.0 [Github (glmmTMB/glmmTMB@6547313 (mailto:glmmTMB/glmmTMB@6547313))], glue 1.3.0 [CRAN (R 3.5.1)], gtable 0.2.0 [CRAN (R 3.5.1)], haven 1.1.2 [CRAN (R 3.5.1)], hms 0.4.2 [CRAN (R 3.5.1)], htmlTable 1.12 [CRAN (R 3.5.1)], htmltools 0.3.6 [CRAN (R 3.5.1)], htmlwidgets 1.2 [CRAN (R 3.5.1)], httr 1.3.1 [CRAN (R 3.5.1)], iterators 1.0.10 [CRAN (R 3.5.1)], jsonlite 1.5 [CRAN (R 3.5.1)], knitr 1.20 [CRAN (R 3.5.1)], lattice 0.20-35 [CRAN (R 3.5.1)], lazyeval 0.2.1 [CRAN (R 3.5.1)], lme4 1.1-17 [url], lmtest 0.9-36 [CRAN (R 3.5.1)], lubridate 1.7.4 [CRAN (R 3.5.1)], magrittr 1.5 [CRAN (R 3.5.1)], MASS 7.3-50 [CRAN (R 3.5.1)], Matrix 1.2-14 [CRAN (R 3.5.1)], memoise 1.1.0 [CRAN (R 3.5.1)], minqa 1.2.4 [CRAN (R 3.5.1)], modelr 0.1.2 [CRAN (R 3.5.1)], modeltools 0.2-22 [CRAN (R 3.5.1)], multcomp 1.4-8 [CRAN (R 3.5.1)], munsell 0.5.0 [CRAN (R 3.5.1)], mvtnorm 1.0-8 [CRAN (R 3.5.0)], nlme 3.1-137 [CRAN (R 3.5.1)], nloptr 1.0.4 [CRAN (R 3.5.1)], nnet 7.3-12 [CRAN (R 3.5.1)], openxlsx 4.1.0 [CRAN (R 3.5.1)], pillar 1.4.0 [CRAN (R 3.5.1)], pkgbuild 1.0.3 [CRAN (R 3.5.3)], pkgconfig 2.0.2 [CRAN (R 3.5.3)], pkgload 1.0.2 [CRAN (R 3.5.3)], plyr 1.8.4 [CRAN (R 3.5.1)], prediction 0.3.6 [CRAN (R 3.5.1)], prettyunits 1.0.2 [CRAN (R 3.5.3)], processx 3.1.0 [CRAN (R 3.5.1)], purrr 0.2.5 [CRAN (R 3.5.1)], pwr 1.2-2 [CRAN (R 3.5.1)], R6 2.2.2 [CRAN (R 3.5.1)], Rcpp 1.0.1 [CRAN (R 3.5.3)], readr 1.1.1 [CRAN (R 3.5.1)], readxl 1.1.0 [CRAN (R 3.5.1)], remotes 2.0.2 [CRAN (R 3.5.3)], rio 0.5.10 [CRAN (R 3.5.1)], rlang 0.3.4 [CRAN (R 3.5.3)], rmarkdown 1.10 [CRAN (R 3.5.1)], rprojroot 1.3-2 [CRAN (R 3.5.1)], rstudioapi 0.7 [CRAN (R 3.5.1)], rvest 0.3.2 [CRAN (R 3.5.1)], sandwich 2.4-0 [CRAN (R 3.5.1)], scales 0.5.0 [CRAN (R 3.5.1)], sessioninfo 1.1.1 [CRAN (R 3.5.3)], sjlabelled 1.0.13 [CRAN (R 3.5.1)], sjmisc 2.7.3 [CRAN (R 3.5.1)], sjstats 0.17.0 [CRAN (R 3.5.1)], snakecase 0.9.1 [CRAN (R 3.5.1)], stringdist 0.9.5.1 [CRAN (R 3.5.1)], stringi 1.1.7 [CRAN (R 3.5.0)], stringr 1.3.1 [CRAN (R 3.5.1)], survey 3.33-2 [CRAN (R 3.5.1)], survival 2.42-3 [CRAN (R 3.5.1)], testthat 2.0.0 [CRAN (R 3.5.1)], TH.data 1.0-9 [CRAN (R 3.5.1)], tibble 2.1.1 [CRAN (R 3.5.3)], tidyr 0.8.1 [CRAN (R 3.5.1)], tidyselect 0.2.5 [CRAN (R 3.5.3)], tidyverse 1.2.1 [CRAN (R 3.5.1)], TMB 1.7.14 [CRAN (R 3.5.1)], usethis 1.4.0 [CRAN (R 3.5.3)], vcd 1.4-4 [CRAN (R 3.5.1)], withr 2.1.2 [CRAN (R 3.5.1)], xml2 1.2.0 [CRAN (R 3.5.1)], xtable 1.8-2 [CRAN (R 3.5.1)], yaml 2.2.0 [CRAN (R 3.5.1)], zip 1.0.0 [CRAN (R 3.5.1)], zoo 1.8-3 [CRAN (R 3.5.1)]
- Date: 2019-10-06

4 Literature

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```
# variance inflation factor modified from https://github.com/aufrank/R-hacks/blob/m
aster/mer-utils.R.
vif.mer <- function (fit) {
  ## adapted from rms::vif
  v <- vcov(fit)
  ## adapt nam  to different usage of names(fixef()) and v to different usage of vc
ov in glmmTMB
  if (class(fit)=="glmmTMB") {
    nam <- names(fixef(fit)[["cond"]])
    v <- v$cond
  } else {
    nam <- names(fixef(fit))
  }
  ## exclude intercepts
  ns <- sum(1 * (nam == "Intercept" | nam == "(Intercept)"))
  if (ns > 0) {
    v <- v[-(1:ns), -(1:ns), drop = FALSE]
    nam <- nam[-(1:ns)]
  }
  d <- diag(v)^0.5
  v <- diag(solve(v/(d %o% d)))
  names(v) <- nam
  v
}
```

Chapter 5

Age-dependent modulation of the arousal response hierarchy during sleep and its reactivity to nighttime transportation noise exposure

Authors
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ABSTRACT

Study Objectives

Frequent arousal responses disrupt the continuity of sleep. To examine a hierarchy in arousal responses during sleep, we systematically compared frequency of occurrence and reactivity to single transportation noise events for four different arousal response markers and modifications with age: single autonomic arousals (AA), cortical arousals (CA), awakenings (AWR), and body movements (MOV).

Methods

A sample of 26 young (19-33 years, 11 women) and 13 older (52-70 years, 7 women) healthy volunteers was examined. Single arousal response events were identified visually from polysomnographic signals (for CA and AWR) or using automatic detection algorithms based on electrocardiogram (ECG) and wrist activity recordings (for AA) or movement recordings from sensors placed below the bed mattress (for MOV). Participants were investigated for six consecutive nights and had two noise-free (first and last night) and four noise exposure nights, two with continuous and two characterized by eventful noise (average sound levels of 45 dB, maximum sound levels between 50 and 62 dB, including road and railway noise).

Results

Frequency of occurrence for the four different arousal response markers depended on the age group: CA rates were higher while AA and MOV rates were lower in the older than in the young individuals. There was no difference between age groups for AWR rates and all-night arousal response rates were unaffected by transportation noise exposure. However, for all four arousal response markers, the probability of an event-related response during eventful road and railway noise exposure nights was significantly higher than spontaneous probabilities. CA reactivity was higher and AA reactivity was lower in the older than in the young individuals reflecting the same pattern as in the all-night rates.

Conclusions

The hierarchy of arousal responses during sleep depended critically on the age group. Event-related arousal probabilities suggested that AA was not the most sensitive arousal response marker and that event-related CA was more likely than event-related AA in the older individuals. This is important given the idea that nighttime noise exposure is considered a cardiovascular risk factor.

1 Introduction

Sleep is not a stable, but a dynamic process (Halasz & Bodizs, 2013). Transient activation phases, so called arousal, disrupt the continuity of sleep as it becomes evident in spontaneous or evoked shifts in electroencephalographic (EEG) rhythms or variations in autonomic nervous system functions, such as alterations in cardiac activity, respiration, or body movements (Halasz et al., 2004; Penzel et al., 2016). These phases are signs of an activated state of the organism, where sleep is temporarily lightened and external information processing and a behavioural reaction of the sleeper becomes more likely (Halasz, 1998; Parrino & Vaudano, 2018). Several markers for arousal responses during sleep exist and basically, include a set of rules to identify distinct, event-like phases with a clear on- and offset (Catcheside et al., 2002; Halasz et al., 2004; Pitson & Stradling, 1998). For example, there is consensus to only consider those shifts in EEG frequency as cortical arousal (CA) that display a desynchronized EEG pattern, defined as an abrupt shift in EEG frequency towards higher frequencies but not spindles (Bonnet et al., 1992). Other arousal response markers are awakenings (AWR), more than 15 s of EEG desynchronization (Berry et al., 2016), autonomic arousals (AA), transient changes in autonomic control such as increases of heart rate (HR) (Griefahn, Brode, et al., 2008; Muzet et al., 2016) or blood pressure (Davies et al., 1993) with a subsequent return to baseline values, or body movements (MOV), above threshold motor activity. Disruption of sleep continuity is considered an integral and essential characteristic of the course of physiological sleep (Akerstedt et al., 2002; Bonnet & Arand, 2007; Halasz et al., 2004), that is even more pronounced with ageing (Bonnet & Arand, 2007; Boselli et al., 1998; Klerman et al., 2013; Yetton et al., 2018), but also occur in response to external stimuli, such as transportation noise (Basner, Glatz, et al., 2008; Basner et al., 2011; Marks et al., 2008; Rudzik et al., 2018; Saremi et al., 2008; Smith et al., 2017).

A hierarchical organization of arousal responses during sleep has been suggested ranging from surges in autonomic nervous system activity (AA) as primary response of the organism, succeeded by CA, and ending with full awakening (Halasz, 1998; Halasz et al., 2004; Levy & Pepin, 2003; Sforza et al., 2000, 1999). While AA demonstrate an isolated transient subcortical increase in sympathetic nerve activity (i. e., HR, blood pressure, etc.), which is not necessarily relayed to the cortex, CA imply cortical involvement, which may also vary according to the cortical area (Nobili et al., 2011; Peter-Derex et al., 2015). Physiologically, during undisturbed sleep, CA are more frequent than AWR (Bonnet & Arand, 2007; Sforza et al., 2004), but only few studies have evaluated AA as distinct events. As AWR and CA often coincide with transient increases in HR (Catcheside et al., 2002; Griefahn, Brode, et al., 2008; Sforza et al., 2000), AA was mainly measured in relation to AWR and CA as a relative increase in HR compared to a pre-event baseline (Azarbarzin et al., 2014; Bonnet & Arand, 1997; Goff et al., 2008; Griefahn, Brode, et al., 2008; Sforza et al., 2000; Togo et al., 2006; Winkelman, 1999; Yang et al., 2006). Building on this co-occurrence and the notion that AA also occur without overt EEG activations (Catcheside et al., 2002; Davies et al., 1993; Guilleminault et al., 2006; S. E. Martin et al., 1997; Pitson, Chhina, Knijn, van Herwaaden, & Stradling, 1994), it can be hypothesized that

AA occur more frequently during the night than both CA and AWR. With respect to reactivity to sensory stimulation, event-related CA probability is much higher than event-related AWR probability, modulated by characteristics of the stimulus (Badia, Harsh, Balkin, O'Rourke, & Burton, 1985; Basner et al., 2011; Smith et al., 2017). The observation that CA but not AA seem to habituate to auditory stimulation during sleep (Basner et al., 2011; N. Carter et al., 2002; Di Nisi et al., 1990; Griefahn, Brode, et al., 2008) corroborates the hypothesis that AA might be a very sensitive marker for arousal responses to auditory stimulation during sleep (Catcheside et al., 2002; Davies et al., 1993; Pitson et al., 1994). But, characteristics of the stimulus, the depth of sleep, or inter-individual differences, such as age of the sleeper, may determine the type as well the sensitivity or threshold of the arousal response (Sforza et al., 1999; Trinder et al., 2012). For example, cardiac reactivity to nighttime noise events was primarily investigated in young individuals (Griefahn, Brode, et al., 2008; Smith et al., 2017).

For the present paper, we evaluated four markers of single arousal responses (i. e. AA, CA, AWR, MOV) that were either identified visually from polysomnographic (PSG) signals (for CA, AWR) or using automatic detection algorithms based on electrocardiogram (ECG) and wrist activity recordings (for AA) and movement recordings from sensors placed below the bed mattress (for MOV). Data were acquired in a sample of healthy young and older individuals that underwent a six-day PSG laboratory study and had two noise-free and four noise nights (four different noise exposure situations with two more continuous and two more eventful noise scenarios). The aim was twofold. As there is little systematic evaluation of the frequency of occurrence of the different arousal response markers in the literature, we compared arousal rates of different markers and further investigated modifications with age. Second, we evaluated the probability of occurrence with transportation noise exposure for each marker to evaluate its reactivity to auditory stimulation. As the autonomic nervous system might be an especially sensitive marker, we were primarily interested in the difference between AA and CA. We hypothesized that frequency of occurrence, both spontaneously as well as event-related, will be highest for AA, followed by CA, and then AWR–at least in the young individuals. There are two competing hypothesis regarding the modification with age. The number of AA might increase with ageing, similarly to CA and AWR, markers of increased sleep fragmentation with ageing (Bonnet & Arand, 2007; Boselli et al., 1998; Klerman et al., 2013; Terzano et al., 2002; Yetton et al., 2018). On the other hand, it is possible that the frequency of occurrence for AA decreases with ageing as heart rate variability (HRV) during wakefulness and sleep physiologically decreases with ageing (Antelmi et al., 2004; Brandenberger et al., 2003; Fukusaki, Kawakubo, & Yamamoto, 2000; van Ravenswaaij-Arts, Kollee, Hopman, Stoelinga, & van Geijn, 1993) and the two might be closely related (Thiesse et al., 2019). The decrease with ageing hypothesis might be further corroborated by age-related modifications in body movements during sleep. Usually, a body movement during sleep is associated with an increase in heart rate, which is related to the magnitude of the movement (Schieber et al., 1971). Age-related decline in body movements during sleep (Gori et al., 2004) might also be evident for AA.

2 Methods

2.1 Participants

Data of thirty-eight healthy volunteers of two age groups (25 young: 19-33 years, 11 women, mean age of 24.6 years; 13 older: 52-70 years, 7 women, mean age of 61.2 years) were included for analyses. This is a subsample of elsewhere published data (Rudzik et al., 2018) and the reasons for reducing the sample size by four participants are outlined below in detail. Participants were free from any acute or chronic illness and current medication as assessed by means of clinical history, physical examination, and routine blood and toxicological urine testing. All had good subjective sleep quality (Pittsburgh Sleep Quality Index (Buysse et al., 1989), PSQI $\leq$ 5) and normal general daytime sleepiness (Epworth Sleepiness Scale (Johns, 1991), ESS $\leq$ 10) and habitually slept between 7 and 9 hours per night. Participants did not have signs of sleep-related breathing disorders, periodic limb movements, or any other indication for a sleep disturbance as confirmed via PSG prior to study admission. All had normal sex- and age-appropriate hearing thresholds. The study was approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, Switzerland, #2014-121) and conformed to the standards of the Declaration of Helsinki. All participants gave written informed consent and received financial compensation for participation. Data acquisition took place between October 2014 and June 2016.

2.2 Protocol and procedure

Participants spent six consecutive nights and days in the sleep laboratory in single windowless, soundproof, and temperature regulated bedrooms under constant ambient lighting levels (between 50-150 lux at the participant's eye during waking periods). During four nights, they were exposed to four different transportation noise scenarios that were applied in an incompletely counterbalanced sequence: scenarios with a more continuous noise characteristic (Road A-B) alternated with scenarios with a more eventful noise characteristic (Road C, Rail D). Another two nights, the first and the last night, were essentially noise-free and served as control nights. Participants had no knowledge about the dynamics of the different transportation noise scenarios but were informed that the first and the last night were essentially noise-free. The sleep episode was scheduled at habitual bedtime for every participant and ended after 8 h. Playback of the acoustical scenarios started with lights off.

Participants were asked to keep a regular sleep-wake cycle with self-selected habitual bed and wake times for one week prior to the study start (nighttime sleep duration 8 ± 0.5 h, no nap taking). Compliance was verified by accelerometers worn at the non-dominant wrist (Actiwatch AW4; Cambridge Neurotechnologies, Cambridge, UK) and self-reported sleep-logs. During one week prior to the study start, they were also asked to restrict consumption of alcohol, caffeinated beverages, and chocolate to moderation to level out effects of these substances on sleep and waking functions.

2.3 Noise scenarios

Five pre-recorded real-world inspired acoustical scenarios were used for playback in the bedrooms during the night: one essentially noise-free (NF) and four transportation noise scenarios (Road A-C, Rail D). Acoustical scenarios differed with respect to noise source (different road traffic situations and railway noise) and noise exposure situation (more continuous, more eventful). Scenario NF ($L_{Aeq,1h}$ of 30 dB at the ear of the sleeper) was played back during the first and the last night. Transportation noise scenarios ($L_{Aeq,1h}$ of 45 dB at the ear of the sleeper) were designed to represent ecologically valid exposure situations. Road A represented a four-lane highway (speed limit of 120 km/h) with approximately 1.000 vehicles per hour at a distance of 400 m. Road B represented a distance of 50 m from a two-lane country road (speed limit of 80 km/h) with approximately 250 vehicles per hour. Road C represented a one-lane urban road (50 km/h) at a 15-m distance with approximately 100 vehicles per hour. Rail D represented a railway noise situation with ten non-overlapping freight and passenger train pass-by events per hour. Rudzik et al. (2018) provide a more comprehensive description of how acoustical scenarios were created.

The audio files were presented through one active monitor loudspeaker (Focal CMS 50, Focal-JMlab, La Talaudière, France) at a 2 m distance to the sleeper's head.

2.4 Sleep recording

Sleep was recorded and scored visually according to standard criteria (v2.3; Berry et al., 2016). PSG recordings were collected using Vitaport-3 digital recorder (TEMEC Instruments B.V., Kerkrade, The Netherlands) with a sampling rate of 256 Hz (storage rate 128 Hz). For EEG arousal scoring, the recommendations of the American Sleep Disorders Association (Bonnet et al., 1992) were adopted; EEG arousal on- and offsets were determined (CA). Awakening, a sleep stage change from any sleep stage to wake, was pinpointed visually as re-occurrence of alpha or faster rhythms; awakening on- and offsets were determined (AWR).

2.5 Movement recording

Movement was recorded using a sensor unit, 16 by 73 cm, which was placed under the bed mattress, approximately below the hip/lumbar region of the sleeper. The sensor unit included eight strain gauges sensors, used for the evaluation of pressure changes, and four piezoelectric sensors, particularly suitable for the measurement of small and dynamic force changes (for a detailed description on integration of signals see Waltisberg, Rudzik, Amft, and Tröster (2018)). A reduced setup of the sensor system, using only strain gauges sensors, proved to be sensitive enough for classification of sleep-disordered breathing and limb movements (Waltisberg, Amft, Brunner, & Tröster, 2017), while the system used here also allowed for an estimation of heartbeat signals (Waltisberg et al., 2018). A synchronization impulse was triggered by the control system of the sensor unit and recorded by the PSG digital recorder so that a precise time synchronization between the two systems was achieved offline. In short, the point in time, when the 1-s moving

standard deviation (SD) of the sensor signals, averaged over all eight strain gauges, exceeded a threshold, was defined as the start and the consecutive undershoot as the end of a movement. The threshold was set manually and was higher than the signal SD during breathing for each night. Three additional parameters were derived to characterize single movements: *MOV duration* (the time in seconds between start and end of a single movement), *MOV intensity* (the SD of the signal between start and end of a single movement), and *MOV displacement* (the absolute centre of gravity difference between start and end of a single movement).

2.6 Autonomic arousal recording

ECG and movement signals (left wrist actimetry) were recorded on Somnotouch-NIBP devices (Somnomedics GmbH, Randesacker, Germany) and synchronized to the PSG recordings. Autonomic arousals, episodes of transient increase in HR with a subsequent return to initial values, with or without concomitant body movements, were detected using the Somno-Art algorithm for sleep and sleep stage scoring based on HR and wrist movement signals (Muzet et al., 2016).

Due to technical difficulties with the respective recording systems, PSG recordings for the evaluation of CA and AWR were available for 246 nights, heart rate and wrist actimetry recordings for the evaluation of AA were available for 222 nights, and sensor signals for the evaluation of MOV were available for 236 nights. We restricted data analysis to those nights with signals from all three sources available and included 215 nights for data analysis. Furthermore, we decided to exclude single nights when the number of the respective arousal response marker was below or above the lower/upper quartile $\pm$ 1.5 times the interquartile range of the respective marker, a robust way to identify outliers (Tukey, 1977). 24 nights were excluded due to outliers: 18 PSG nights had outlier (15 nights for CA and 3 nights for AWR), 5 nights had AA outlier, and 14 nights had MOV outlier. There was a certain overlap as in some nights, decision to exclude was based on above-threshold values in more than one arousal response marker. In total, we analysed 191 nights. Figure 5.1 gives an overview of included participants and nights.

2.7 Data analysis

Arousal rates for different markers

Per definition, CA and AWR can only occur from sleep. CA require a minimum of 10 and AWR at least 15 continuous seconds of sleep to be classified accordingly (Berry et al., 2016). As the scoring of MOV and AA based on continuous signals, single events were also detected during phases of intra-sleep wakefulness. To compare the different arousal response markers, MOV and AA were restricted to also only occur from sleep (i. e., preceded by a minimum of 15 continuous seconds of sleep). Linear mixed models were used for statistical analysis, which included random subject effects to account for the repeated measurements within participants. The dependent variable was the number of the respective arousal response marker per hour of TST (n/h TST). We included as independent variables in the model: noise exposure (five levels according to the different noise scenarios), age (two levels: young vs. older), and arousal

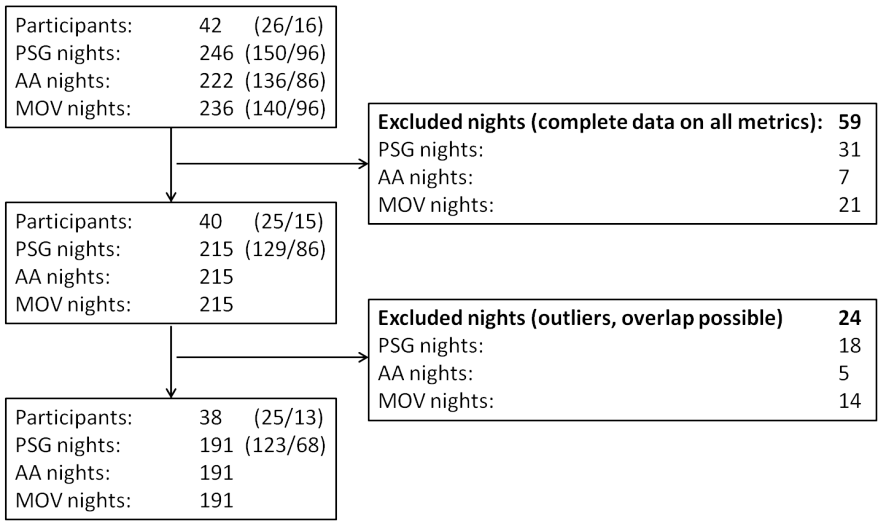

Figure 5.1: Flow diagram of the selection of participants, nights, and arousal response marker. In parenthesis are the number of individuals or nights in the young and older subgroups. PSG refers to polysomnography; autonomic arousal (AA); body movement (MOV).

response marker (four levels: AA vs. CA vs. AWR vs. MOV), and all possible interactions. In a second step, we tested whether differences between arousal response markers were present during every night. We did this as differences between group means do not necessarily imply significant differences on the individual level (Trafimow, 2014). All analyses were performed in R (R Core Team, 2018) and models were fitted using the *afex* library (v0.18-0; Singmann et al., 2017). Significance of fixed effects was evaluated using F-tests with type 3 sums of squares. Denominator degrees of freedoms were approximated using the Kenward-Rogers or Satterthwaite procedure. For post-hoc testing (marginal effects, interactions, and pairwise comparisons), we used the *lsmeans* package (v2.26-3; Lenth, 2016) and adjusted p-values for multiple comparisons (Tukey method).

MOV-AA co-occurrence

As MOV and AA are closely related (Schieber et al., 1971; Townsend, Johnson, Naitoh, & Muzet, 1975; Winkelman, 1999), we were further interested in a description of MOV-AA co-occurrence for a cross-validation of the AA algorithm performance. A single MOV or AA was considered to be co-occurring if there was a temporal overlap between single MOV and AA on- and offsets. It is to be expected that co-occurrence depends on MOV magnitude with higher intensity MOV (MOV duration, MOV intensity, MOV displacement) more likely to be associated with AA.

Event-related arousal probability

Arousal responses were related to distinct, well defined pass-by events for the two more eventful noise scenarios. For time synchronization with the PSG, the reproduced sound in the bedroom was recorded continuously using a microphone and logged with the PSG recording device.

Road C included 400 single road noise events that differed according to duration (16.6-58.8 s), maximum sound pressure level (SPL) (52.6-62.4 dB, mean: 55.9 dB), and maximum slope of the SPL (2.4-6.4 dB/s). Rail D included 80 single railway noise events that differed according to duration (16.9-113.7 s), maximum SPL (50.1-61.7 dB, mean: 57.5 dB), and maximum slope of the SPL (0.7-5.2 dB/s). All reported acoustical metrics are based on A-weighted SPL. We defined an arousal response to be event-related when its onset occurred within the time span of a single noise event (event duration + 5 s). Event-related arousal probabilities were calculated as ratios between the number of event-related arousal responses and the number of adequate noise events. A noise event was considered adequate when it occurred after the first onset of stage 2 non-rapid eye movement (NREM) sleep, not during intra-sleep wakefulness, and when there was no sleep disruption prior to noise onset, awakening within 30 s or EEG arousal within 10 s (Basner et al., 2011; McGuire et al., 2016). But, an arousal response might not be truly event-related and could have occurred spontaneously at the same time. Consequently, there is consensus in the literature to adjust event-related arousal probabilities using spontaneous arousal probabilities to account for spontaneous fluctuations (Basner et al., 2011; Brink et al., 2009; Griefahn, Brode, et al., 2008; McGuire et al., 2016; Smith et al., 2017). Spontaneous arousal probabilities were derived from "virtual" events, i. e. periods during the first noise-free night corresponding to single noise events during the two eventful noise exposure nights subjected to the same aforementioned exclusion criteria. The adjusted event-related arousal probability was calculated by subtracting spontaneous from event-related values according to Brink et al. (2009). This was analyzed statistically using mixed effects logistic regression models with the dependent binary variable arousal during noise/"virtual" event (1) or no such activation (0). The factors condition (event-related vs. spontaneous), age (young vs. older), and noise source (road vs. railway noise exposure) were included as predictors in the models. Logistic regression models were fitted using the *lme4* library (v1.1-17; Bates et al., 2015), significance of fixed effects was tested using Wald chi-square tests via the *car* package (v3.0-0; Fox & Weisberg, 2011), and post-hoc testing was performed with the *lsmeans* package (v1.2.3; Lenth, 2016).

3 Results

3.1 Rates for different arousal response markers

Table 5.1 gives a summary of standard all-night sleep variables.

There was a significant interaction between age and arousal response marker ($F_{3,688} = 78.20, P < 0.001$; see Figure 5.2). In the young individuals, all rates were significantly different between arousal response markers (Tukey post-hoc test, $P < 0.001$ for all comparisons) except for the difference between CA and MOV ($P = 0.16$). In the older individuals, all rates were significantly different between arousal response markers ($P < 0.001$ for all comparisons) except for the difference between AA and MOV ($P = 0.17$). AA and MOV rates were significantly lower ($P < 0.001$ for AA; $P = 0.01$ for MOV), while CA rates were significantly higher in the older compared to the young individuals ($P < 0.001$), and AWR rates did not differ significantly

Table 5.1: All-night standard macro- and microstructure sleep variables according to the respective age group

Variable	Young individuals (N = 25; 123 nights)	Older individuals (N = 13; 68 nights)
TST (min)	455.2 ± 16.9	422.6 ± 36.7
SE (%)	94.8 ± 3.5	88.0 ± 7.6
Sleep latency N1 (min)	10.1 ± 8.1	11.2 ± 8.6
Sleep latency N2 (min)	16.6 ± 9.5	16.9 ± 9.4
SWS latency (min)	28.7 ± 10.0	41.9 ± 22.1
REM latency (min)	68.0 ± 23.4	70.4 ± 27.5
Intra-sleep wake (% of TST)	2.9 ± 3.0	10.2 ± 8.7
N1 (% of TST)	12.6 ± 3.4	17.1 ± 4.5
N2 (% of TST)	47.4 ± 6.0	53.8 ± 6.7
SWS (% of TST)	17.1 ± 6.4	7.9 ± 6.1
REM (% of TST)	22.9 ± 4.4	21.2 ± 5.4
EEG Arousal rate (n/h TST)	10.7 ± 3.8	15.0 ± 4.2
EEG Arousal rate (n/h NREM)	10.2 ± 4.2	14.2 ± 4.5
EEG Arousal rate (n/h REM)	12.6 ± 6.2	18.7 ± 9.4
Awakening rate (n/h TST)	1.5 ± 0.9	2.4 ± 1.1
Awakening rate (n/h NREM)	1.4 ± 1.0	2.4 ± 1.3
Awakening rate (n/h REM)	2.1 ± 1.9	2.1 ± 1.7

Note. Means ± standard deviations. TST refers to total sleep time; SE: sleep efficiency = TST/TIB; TIB: time in bed (480 min).

between age groups ($P = 0.26$). Rates did not differ with noise exposure ($F_{4,694} = 0.64, P = 0.64$); all interactions with noise exposure were non-significant ($P > 0.88$).

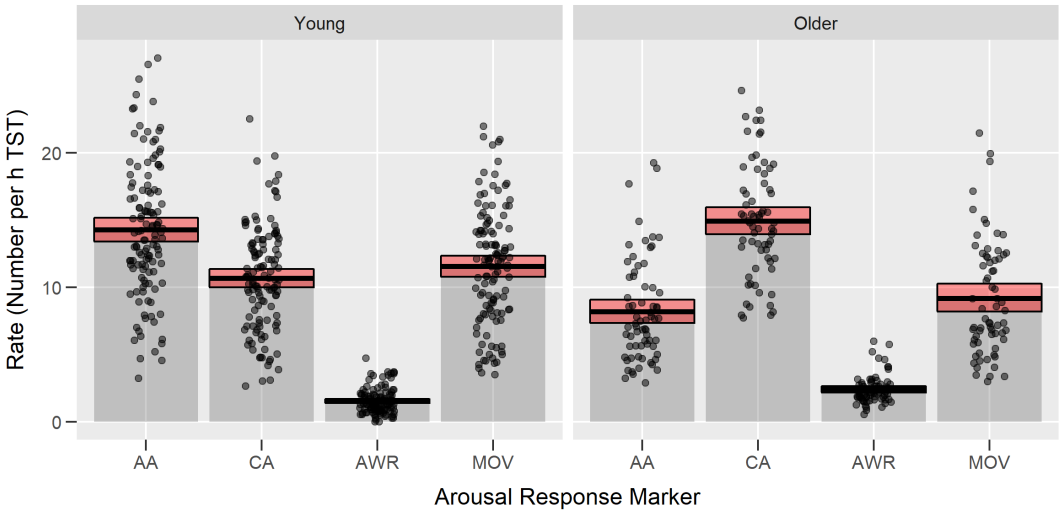

Figure 5.2: Rates (number per h TST) for the different arousal response markers autonomic arousal (AA), cortical arousal (CA), awakening (AWR), and body movement (MOV) pooled for all nights (N = 191 nights). Each dot represents raw values per night, bars represent mean values, and bands around bars represent 95 % confidence intervals.

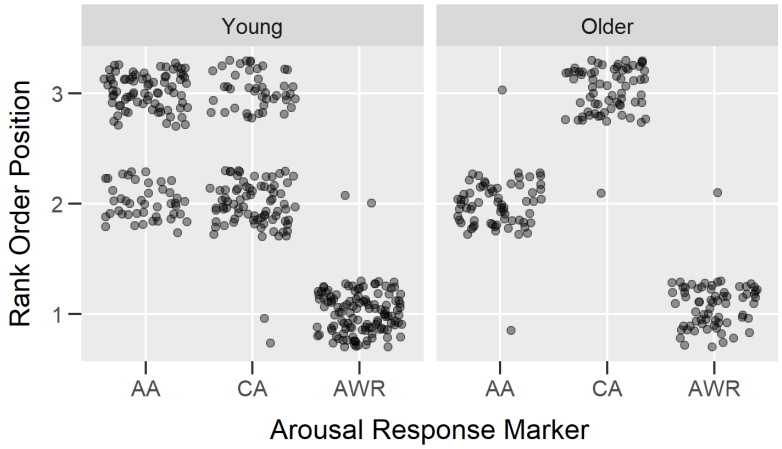

Figure 5.3: Ranking within single nights (N = 191 nights) of rates (number per h TST) for the different arousal response markers autonomic arousal (AA), cortical arousal (CA), and awakening (AWR). Rank order position 1 represents the marker with the lowest rate and 3 the marker with the highest rate within single nights, respectively.

As the described differences in rates between arousal response markers based on mean values, we were further interested whether the differences were present during every single night. We ranked rates of three arousal response markers (AA, CA, AWR) within single nights: the arousal response with the lowest rate within a single night is ranked to position 1, while the one with the highest rate is ranked to position 3 (discrete variable rank order position; Figure 5.3). As MOV and AA often co-occur (see also below) and MOV was not significantly different from AA in the older and from CA in the young individuals, MOV was not included in this analysis. In the young individuals, arousal response markers were ranked according to the pattern AWR (rank 1) < CA (rank 2) < AA (rank 3) in 62.60 % of the nights ($N = 77$) and according to the pattern AWR < AA < CA in 35.77 % of the nights ($N = 44$); only 1.63 % of nights ($N = 2$) had a different sequence. In the older individuals, arousal response markers were ranked according to the pattern AWR < AA < CA in 97.06 % of the nights ($N = 66$), while only 2.94 % of nights ($N = 2$) had a different sequence.

3.2 MOV-AA co-occurrence

The relationship between AA and MOV was not reciprocal. While 77.64 % of MOV coincided with AA, only 65.90 % of AA coincided with MOV. This difference was mainly driven by age. While the relationship was somewhat balanced in the older (i. e., approximately 25 % of MOV and AA, respectively, occurred not in accordance with the other metric), in the young, a large proportion of AA, 37 %, occurred without an associated body movement (Figure 5.4).

In addition, MOV-AA co-occurrence depended on the magnitude of the body movement. For all three investigated magnitude parameters describing single MOV (duration, intensity, displacement), there was the clear picture that higher intensity MOV were more likely to be associated with AA (Figure 5.5). Body movements, simultaneously occurring with an AA were

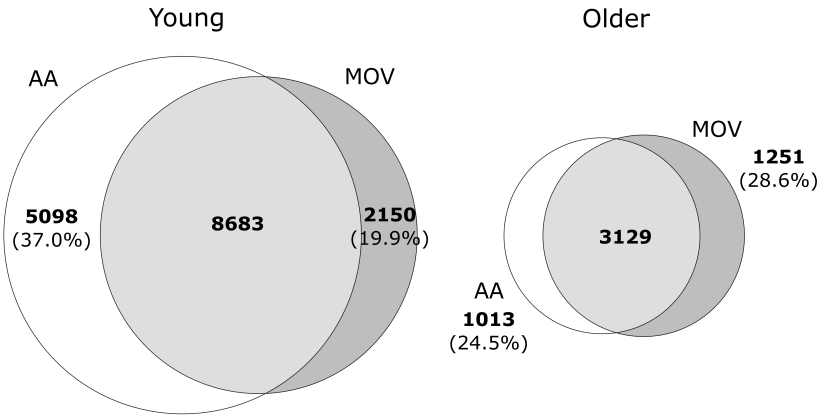

Figure 5.4: Venn diagrams for body movement (MOV) and autonomic arousal (AA) co-occurrence in young and older individuals. The percentages refer to the part of total AA and MOV within age groups, respectively, that were not co-occurring with the opposite arousal marker. Please note that the interpretation of the absolute circle sizes is not meaningful in this figure as the number of included nights differed between young and older individuals: $N = 123$ nights in the young and $N = 68$ nights in the older individuals.

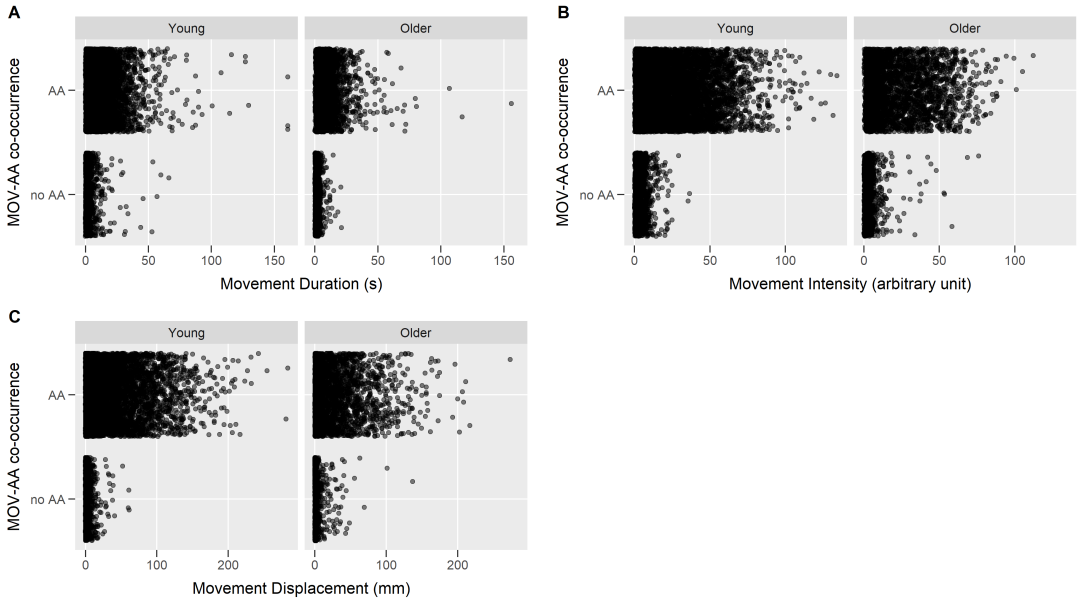

Figure 5.5: Description of single body movements (MOV; N = 15,213 MOV). Displayed are the three magnitude parameters MOV duration **(A)**, MOV intensity **(B)**, and MOV displacement **(C)** in young and older individuals depending on whether an autonomic arousal (AA) was identified simultaneously (AA) or not (no AA). Displayed are jittered raw values.

longer ($F_{1,15198} = 1,273.82, P < 0.001$), had a higher intensity ($F_{1,15207} = 1,919.85, P < 0.001$), and the movement-related center of gravity displacement was higher ($F_{1,15206} = 1,083.20, P < 0.001$) than for MOV without an associated AA. There was no interaction with age ($P > 0.05$ for all F-values of the respective interaction with age).

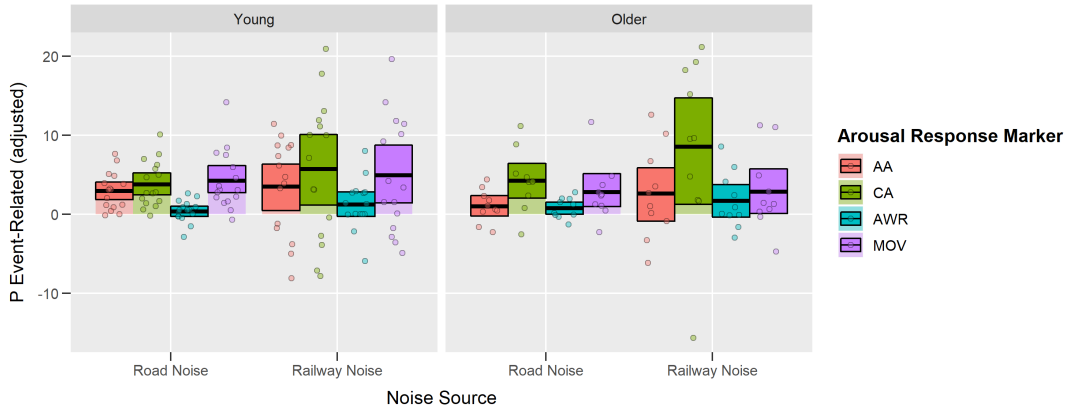

Figure 5.6: Adjusted event-related arousal probabilities for the different arousal response markers. Autonomic arousal (AA), cortical arousal (CA), awakening (AWR), and body movement (MOV) for the two nights with eventful noise exposure, one including road and the other railway noise. Each dot represents single values, bars represent the mean, and bands around bars represent 95 % confidence intervals.

3.3 Event-related arousal probability

From a total of 13,264 adequate single road and railway noise events (eventful noise exposure nights with 63 nights), 1,926 single noise events (14.52 %) were associated with an AA, 2,034 events (15.33 %) with a CA, 1,773 events (13.37 %) with a MOV, and 338 events (2.55 %) with an AWR. For all four arousal response markers, arousal probabilities were significantly higher during the two eventful noise exposure nights than the spontaneous probabilities determined from the first noise-free night ($P < 0.001$ for all χ^2-values for the factor condition). Figure 5.6 displays adjusted event-related probabilities, i. e. the arousal probability during the respective exposure nights minus the spontaneous arousal probability during the first noise-free night. Odds ratios (event-related vs. spontaneous, respectively) increased in the rank-order AA (1.23), AWR (1.37), CA (1.50) = MOV (1.50). Event-related AA probability was higher in young than in older individuals ($\chi^2 = 13.43, P < 0.001$), event-related CA was higher in older than young individuals ($\chi^2 = 20.99, P < 0.001$), while there were no significant differences for event-related MOV and AWR probabilities between age groups (MOV: $\chi^2 = 2.44, P = 0.12$; AWR: $\chi^2 = 2.61, P = 0.11$). For all four arousal response markers, arousal probabilities were significantly higher for railway than for road noise exposure ($P < 0.001$ for all χ^2-values for the factor noise source). But, there were no significant interactions between condition and noise source indicating that the observed differences between road and railway noise exposure was independent of the actual noise exposure (see discussion).

4 Discussion

The present paper aimed at comparing four different arousal response markers (EEG arousal (CA), awakenings (AWR), autonomic arousal (AA), and body movements (MOV)) with respect

to frequency of occurrence and reactivity to single transportation noise events. The main results of the present study were as follows: 1) frequency of occurrence during all nights depended on the age group: while CA rates were higher in the older than in the young, AA and MOV rates showed the reversed pattern. 2) For all four arousal response markers, the probability of an event-related arousal was significantly higher than spontaneous probabilities with AA reactivity being higher in the young than in the older and CA reactivity being higher in the older compared to the young individuals.

Both all-night AA rates as well spontaneous and event-related AA probabilities were lower in older compared to young individuals so that we were not able to demonstrate a response hierarchy of different arousal markers independent of age. In the young subgroup, we observed that on average AA occurred more frequently during the night than CA. We did not evaluate AA-CA co-occurrence explicitly, but the results still suggest that a part of AA occur without a concomitant CA. This is consistent with the literature as 35.3 % (Basner et al., 2007) or 28 % (Olsen et al., 2018) of all automatically HR identified AA had no co-occurring CA. Nevertheless, we observed two different AA-CA-AWR ranking patterns in the young: 62.60 % of nights had more AA than CA, while 35.77 % of nights had more CA than AA. While in the majority of the nights, AA were more frequent than CA, the difference in the ranking pattern suggests high inter-individual and -night variability in cardiac autonomic control as well as in thresholds for the different arousal responses. In the older individuals, we found that CA were more frequent than AA both on average and during almost every single night suggesting that in the older a part of CA is not accompanied by an AA, at least with the threshold used by our detection algorithm. The only experiment, to our knowledge, that reported on frequency of occurrence for both CA and AA was done in non-healthy individuals with an age range between 24 and 50, that were under evaluation of possible sleep-disordered breathing (Pitson & Stradling, 1998). CA were more numerous than AA, defined as transient HR increases greater than 10 beats per minute (Pitson & Stradling, 1998). Even though the absolute rates were higher as both CA and AA increase with sleep disordered breathing (Chugh et al., 1996; Poyares et al., 2002), the relationship between markers was similar than the one we found, at least in the older. Our finding is not consistent with the view that arousal responses during sleep originate from a unique neurophysiological process where a subcortical arousal, a HR increase identified as AA, precedes the cortical arousal, CA or AWR (Levy & Pepin, 2003; Sforza et al., 2000). Sforza et al. (2000) demonstrated that every CA was associated with a significant HR increase, preceding the visual CA onset by two beats; that AA precede the onset of CA was also demonstrated by others (Bonnet & Arand, 1997; Gosselin, Michaud, Carrier, Lavigne, & Montplaisir, 2002; Togo et al., 2006). There are two explanations for the finding that a part of CA occurred without a concomitant AA. Detection of AA was performed on the basis of HR signals without processing of cortical EEG signals at that stage of the analysis. We defined AA as a transient event, meaning that every above-threshold increase in HR with a subsequent return to baseline values was scored as an AA by our automatic detection algorithm (Muzet et al., 2016). Others, however, used cortical EEG signals as a basis and evaluated based on detected cortical events increases in cardiac activity compared to a pre-event/-state baseline (Sforza et al., 2000). A part of CA

associated HR increases might been missed by our approach when this increase did not meet the threshold. Methodologically, other AA events might have been missed by our algorithm when a HR increase was not followed by a subsequent HR deceleration, violating the definition of a transient event. It is possible that a cortical arousal reaction leads not only to a phasic but a tonic activation of the ANS, resulting in a several minutes lasting HR increase without a return to the pre-arousal level, impeding the detection of single events. This might also depend on the time of the night as cortical arousal reactions were demonstrated to be more numerous during the beginning and the end of ultradian sleep cycles (Rudzik et al., 2019) when mean heart rate, at least for the end of a cycle, is increasing rapidly when sleep progresses towards REM sleep (Cajochen et al., 1994).

The observed age-dependent modulation of the frequency of occurrence of the arousal response might reflect age-related changes in autonomic nervous system functions. Normative ageing is associated with a decrease in HRV both during wakefulness (Antelmi et al., 2004; Fukusaki et al., 2000; van Ravenswaaij-Arts et al., 1993) and during sleep (Brandenberger et al., 2003; Viola et al., 2011) as a consequence of changes in parasympathetic modulation (Jandackova, Scholes, Britton, & Steptoe, 2016). Detection of single AA and HRV might be closely related: higher physiological fluctuations in the beat-to-beat interval length will result in a higher probability for detecting episodes of transient increases in HR with a subsequent return to initial values (our definition of AA). On the other hand, also others found an attenuation of the autonomic arousal response during sleep in older individuals (Goff et al., 2008; Gosselin et al., 2002; Okada, Hanyu, Noda, Kayukawa, & Ohta, 1998). While CA were associated with a maximal HR increase of 8.7 beats per min (bpm) in young individuals (age between 20 and 35 years), CA in older individuals (50-65 years) were associated with a HR increase of 4.2 bpm (Gosselin et al., 2002). Similarly, in patients with sleep disordered breathing, only 56.5 % of all sleep apnea/hypopneas events were terminated by an AA in the older ($>$ 60 years) as compared to 88.9 % in middle-aged individuals (40-60 years) (Okada et al., 1998). Consequently, the coupling between the autonomic and the central nervous system during sleep might be modified with advancing age (see also de Zambotti, Trinder, Silvani, Colrain, & Baker, 2018). In both age groups, AWR rates were lower than CA, AA, or MOV rates which is well in line with the literature (Basner, Glatz, et al., 2008; Bonnet & Arand, 2007). Awakenings are rare events during sleep and occur at a rate between 2.94 and 7.26 per hour TST depending on the age group (Bonnet & Arand, 2007).

Our results show that AA reactivity with single transportation noise events was higher than CA reactivity in the young, while older age was associated with the reversed pattern. This finding is surprising as AA were considered a very sensitive marker for arousal responses to auditory stimulation during sleep (Catcheside et al., 2002; Davies et al., 1993; Pitson et al., 1994). Keefe et al. (1971) underwent a systematic evaluation of thresholds, in terms of sound intensity required to elicit a response in different peripheral, autonomic, and central arousal response markers and demonstrated an arousal threshold hierarchy with central preceding autonomic responses by about 10 dB in young healthy individuals. Adjusting for spontaneous probabilities that were higher for AA than for AWR responses, Basner, Müller, Elmenhorst, Kluge, and

Griefahn (2008) demonstrated that additional arousal probabilities did not differ between AA and AWR suggesting that there were no differences in sensitivity or reactivity to single aircraft noise events. AA play an important role for the evaluation of nighttime noise effects on health as it was hypothesized that repeated nighttime noise induced AA contribute to the development of cardiovascular risk factors or cardiovascular diseases observed in epidemiological field experiments (Griefahn, Brode, et al., 2008; Münzel et al., 2014). The majority of experimental studies included young healthy individuals to evaluate cardiac reactivity to noise during sleep using either artificial sounds (N. Carter et al., 2002; Catcheside et al., 2002; Davies et al., 1993; Di Nisi et al., 1990; Guilleminault et al., 2006; Nalivaiko et al., 2007) or transportation noise (Griefahn, Brode, et al., 2008; Hofman, Kumar, & Tulen, 1995; Smith et al., 2017). Tassi et al. (2010) used a broader age range and found higher reactivity to single railway noise events in young (mean age of 26 years) than in older individuals (mean age of 52 years) for percentage of noise events with an HR increase of at least 8 bpm and the heart response amplitude. Similarly, using a wide age range between 18 and 71 years, Basner et al. (2011) reported that the transportation noise events induced heart rate change decreased with ageing. Attenuated cardiac reactivity to auditory stimuli might reflect reduced coping with environmental stressors with advanced age (Struzik, Hayano, Soma, Kwak, & Yamamoto, 2006). On the other hand, it was hypothesized that not the frequency but the magnitude of autonomic activations constitute the cardiovascular burden of arousal responses during sleep (Levy & Pepin, 2003; Trinder et al., 2012). Autonomic activation intensity showed substantial inter-individual variability: for a given arousal intensity, CA associated HR increases ranged from 4.1 to 18.1 bpm (Azarbarzin et al., 2015). Individuals with large cardiovascular activations at spontaneous, sleep disorder-related, or transportation noise induced arousals might be particularly at risk for the development of cardiovascular risk factors or diseases (Trinder et al., 2012).

The all-night arousal rates were not consistently increased with noise exposure, but event-related arousal probabilities were significantly higher during the two eventful noise exposure nights than the spontaneous probabilities determined from the first noise-free night. Clustering of arousal responses around single noise events in the absence of additional reactions (i. e., all-night rates were stable) suggest a redistribution of arousal responses which only replace spontaneous arousal on the absolute all-night level. This argument was first put forward by Muzet, Naitoh, Johnson, and Townsend (1974) who observed that approximately 50 % of all-night body movements, during both NREM and REM, occurred in proximity of 80-92-dB tone pulses in the absence of an all-night increase in body movements during noise exposure nights. Similarly, Basner et al. (2011) reported that a fair amount of event-related activation reactions replaced spontaneously occurring ones: up to 93 % for awakenings and up to 67 % for CA.

There is substantial debate in the literature whether the source of the nighttime transportation noise affects the arousal response. There is evidence that event-related awakening probability is higher for single railway than for road and air traffic noise events (Basner et al., 2011; Elmenhorst, Griefahn, Rolny, & Basner, 2019; Marks et al., 2008). But rather than the transportation traffic mode per se, event-related arousal probabilities (including awakenings, CA, or HR increases) were demonstrated to increase with various acoustical characteristics of single transportation

noise events, such as increasing maximum SPL, slope of rise of the SPL, and duration of single noise events (Basner et al., 2011; Elmenhorst et al., 2012; Griefahn, Brode, et al., 2008; Marks et al., 2008; Rudzik et al., 2018; Tassi et al., 2010). The increased probability, both spontaneous and event-related, observed for all arousal markers during railway as compared to road noise exposure nights is more likely an artefact than an interpretable effect and might be attributed to the very different number of included noise events (actual noise or "virtual" events) of 400 for the road and 80 for the railway noise exposure nights. When the all-night number of arousal responses is fixed, it is obvious that searching 400 time windows for an event-related arousal response will result in a lower probability than searching 80 time windows, irrespective of whether this was done for "virtual" or actual noise events. In the same vein, precision of the estimates, as indicated from lower inter-individual variability (i. e., range and confidence intervals) was higher for road than railway noise exposure nights, which is to be expected from the profound difference in sample size (i. e., number of single noise events) between the two eventful noise exposure nights. Only 15.33 % of single transportation noise events were associated with a CA meaning that 84.67 % of single road or railway noise events did not elicit a CA in the sleeping individuals. This is in agreement with the literature: Smith et al. (2017) reported that around 15 % of single railway noise events were associated with a CA (32 and 52 noise events per night), while Saremi et al. (2008) found that 3-45 % of single railway noise events caused a CA (16 noise events per night), depending on the type of the train as well as the maximum SPL. Furthermore, they reported a strong dependency on the sleep stage with event-related CA being more prevalent during NREM (N2 sleep and SWS) compared to REM sleep (Saremi et al., 2008).

In the literature, there is no consensus regarding the exact definition of an AA and there are no clear-cut criteria for duration and amplitude of a HR increase to account as an AA (Basner, Müller, et al., 2008). Additionally, the term autonomic arousal is not used in a systematic way. For some, every transitory increase in sympathetic activity during the night, irrespective of EEG arousals, is an autonomic arousal (integrative perspective), which was evaluated on the basis of HR (Basner et al., 2007; Olsen et al., 2018), blood pressure (Davies et al., 1993), or pulse transit time (Pitson & Stradling, 1998; Stradling et al., 2000). For others, only transitory increases in sympathetic activity that occur without overt EEG arousals are autonomic arousal (exclusive perspective) (Penzel et al., 2016). Here, we followed the integrative perspective and included all transitory increases in sympathetic activity as indexed by a HR increase, so that an overlap in arousal marker was possible, i. e., a co-occurrence of AA and CA or AWR. Several strategies were suggested for the validation of autonomic markers (Levy & Pepin, 2003). The basic principle is to compare AA with other well-defined or reliable events or scores using correlations or other performance markers. Events or scores to compare to may include: 1) CA, adopting the ASDA or other definitions of cortical activations; 2) events underlying sleep fragmentation, such as external noise or respiratory events during sleep; or 3) daytime symptoms, such as subjective sleepiness. The first option might be misleading as there might be false positives (AA present, CA not present) that still represent genuine AA. Olsen et al. (2018) showed that 43 % of false positives actually coincided with a respiratory event and 38 % with a leg movement suggesting

that the occurrence of potentially sleep disrupting events may cause an autonomic activation in the absence of a visually discernible EEG activation. We adopted the second strategy and compared transportation noise event-related AA and CA probabilities. Odds ratios for AA were lower than for CA indicating a higher sensitivity for CA to detect noise event-related sleep fragmentations. However, this difference is likely to be age-related, even though there was no significant interaction between age and condition, AA probabilities were lower in the older, both event-related and spontaneous. We performed an additional validation for our AA detection using body movements which are known to be associated and preceded by HR increases (Schieber et al., 1971; Townsend et al., 1975). There was a good agreement between AA and MOV detection as 65.90 % of AA coincided with a body movement. Moreover, AA associated body movements were longer, had a higher intensity, and a larger center of gravity displacement. MOV-AA co-occurrence significantly varied with age as the agreement was higher in the older than in the young individuals; MOV also were decreased with advancing age which is consistent with the literature (Gori et al., 2004). One limitation of our approach was the reliance on visual examination of EEG signals to classify EEG responses as CA. Consequently, it was demonstrated that the acquisition and interpretation of the quite arbitrary ASDA scoring criteria for manual evaluation resulted in considerable variability and low agreement between different human scorers (Bonnet & Arand, 2007; Drinnan, Murray, Griffiths, & Gibson, 1998). Similar to the automatic detection of AA and MOV events performed in our experiment, an automatic EEG arousal detection algorithm would ensure reliable, objective, and reproducible results; however, automatic CA detection is still in its infancy but demonstrated promising performance recently (Alvarez-Estevez & Fernandez-Varela, 2019).

In conclusion, ranking of arousal responses during sleep depended critically on the age group. While in the young, frequency of occurrence for AA and CA responses complied with the view of a common generator of arousal responses during sleep forming a hierarchy with AA being the first arousal response, results in the older suggest that a substantial part of cortical arousal reactions occurred in the absence of autonomic activation which might reflect age-related decline in parasympathetic modulation during sleep. Event-related arousal probabilities suggested that AA was not the most sensitive arousal response marker and that especially in the older, who are more at risk for cardiovascular disease, event-related CA were more likely than event-related AA. Whether magnitude rather than frequency of occurrence of the cardiac arousal response constitutes cardiovascular burden of arousal responses during sleep will require future investigation.

Chapter 6

Additional Results

In the following, several results will be outlined that were not included in any other publication but were still important for the understanding of noise effects on sleep. This includes subjective sleep quality and subjective sleepiness ratings as well as an in-depth analyses of observed effects on REM sleep. Furthermore, a description of acoustical characteristics of noise events recorded under field conditions was included for illustrative purposes.

All analyses were performed in R (R Core Team, 2018). Mixed models were fitted with lme4::lmer via the *afex* package (v0.18-0; Singmann et al., 2017). Denominator degrees of freedoms for all effects were approximated using the Kenward-Rogers procedure. Type 3 sums of squares were used. Post-hoc tests and planned contrasts were run using the *lsmeans* package (v2.26-3; Lenth, 2016): p-values were adjusted using an approximation of the Dunnett or the Tukey adjustment, depending on the type of comparison.

1 Subjective sleep quality

Immediately after each sleep episode (approx. 5-10 min after waking up), subjective sleep quality was assessed using the Leeds Sleep Evaluation Questionnaire (Parrott & Hindmarch, 1978). Participants indicated answers on verbally anchored visual analog scales comparing the preceding sleep episode to usual sleep. The eight used items assessed the following four domains of sleep quality: getting to sleep (anchors: more difficult–easier than usual; slower–more quickly than usual; less sleepy–more sleepy than usual); quality of sleep (anchors: more restless–calmer than usual; with more wakeful periods–with less wakeful periods than usual); awake following sleep (anchors: more difficult–easier than usual; requires a period of time longer–shorter than usual); and behaviour following upon awakening (anchors: tired–alert). Additionally, questions about subjective sleep latency (minutes), number of remembered awakenings, duration of intra-sleep wakefulness (minutes), total sleep time (minutes), and one question about global sleep quality ("Taken everything together, how well did you sleep?") were asked. Subjective sleep quality data were analyzed using linear mixed-effects models with a random intercept for the participant, the within-participant factor noise exposure scenario (noise-free baseline night vs. Road A vs. Road B vs. Road C vs. Rail D vs. noise-free recovery night), the between-participant factor age group (young vs. older), and the interaction between the two factors. Planned orthogonal contrasts were used to test the difference between the pooled two noise-free nights and pooled four noise exposure nights, the pooled noise-free nights and the individual noise exposure nights, and finally, the first and the last night to test the effect of the

time in the experiment on all outcome variables; each contrast testing was done in separate for both age groups.

Noise reduced global subjective quality of sleep ($F_{5,167} = 3.57, P = 0.004$), irrespective of age: this was observed for the planned contrasts for pooled noise exposure ($P < 0.001$, Dunnett's test) and for all road noise exposure nights (Road A, Road B, and Road C) on the individual noise contrast level ($P < 0.05$, Dunnett's test).

The noise-induced reduction in subjective sleep quality was mirrored in an increase in the number of remembered awakenings, which was especially evident in the young individuals (pooled noise exposure: 2.55 versus 3.15, $P = 0.048$, Dunnett's test). Duration of subjective intra-sleep wakefulness was higher in older compared to young individuals ($F_{1,39} = 8.77, P = 0.005$) and further increased over the course of the experiment (difference between the first and the last experimental night: 33.60 vs. 58.01 min, $P = 0.014$, Dunnett's test). Moreover, subjective TST decreased during noise exposure nights in the older individuals (pooled noise exposure: 437.13 vs. 420.39 min, $P = 0.037$, Dunnett's test; for Road C on the individual noise contrast level: 437.13 vs. 408.76 min, $P = 0.049$, Dunnett's test).

2 Subjective sleepiness

To assess subjective sleepiness, the Karolinska Sleepiness Scale (KSS) was used (Gillberg, Kecklund, & Akerstedt, 1994). Participants were asked to evaluate their level of sleepiness in the past 10 minutes on a nine-point verbally anchored Likert-type scale that ranged from 1 (extremely alert) to 9 (very sleepy–fighting sleep) twenty times during scheduled wakefulness. In the mornings (i. e., until 185 minutes after habitual wake up time, 7 ratings) and evenings (i. e., five hours prior to habitual sleep time, 10 ratings), participants were asked at 30-min intervals and every two hours during the day in between (3 ratings). We used linear mixed-effects models and included three different models. 1) Our first model contained the main effects age group (young vs. older), time-of-day (20-level factor), the interaction between the two, and a random subject effect. 2) The second model contained the main effects age group (young vs. older), noise exposure scenario (noise-free baseline night vs. Road A vs. Road B vs. Road C vs. Rail D vs. noise-free recovery night), the interaction between the two, and a random subject effect; 20 separate models were run at every time of day individually. 3) The third model contained the main effects day (day 1 vs. day 5), time-of-day (20-level factor), all possible interactions, and a random subject effect; two different models were run separately for each age group. We ran this third analysis to test for cumulative noise effects after four nights of noise exposure.

1) We observed a significant two-way interaction for age and time-of-day ($F_{19,4366} = 3.32, P < 0.001$) on subjective sleepiness ratings; during each point in time older indicated lower sleepiness than young individuals, which was significant for all morning ratings (rating 1-7 until 185 minutes after habitual wake up time, for all $P < 0.05$).

2) In the older group, we observed an increased subjective sleepiness during the first 30 min after the final awakening in the morning after noise exposure nights (two ratings, i. e. immediately after awakening and 30 min after: pooled noise exposure, all $P < 0.05$, Dunnett's test;

for Road B on the individual noise contrast level, all $P < 0.05$, Dunnett's test). In the young subgroup, subjective sleepiness upon the final awakening in the morning was increased until 120 min later after noise exposure nights (four ratings, i. e. immediately after awakening and three additional half-hour ratings: pooled noise exposure, all $P < 0.05$, Dunnett's test; for Road A and Rail D on the individual noise contrast level, all $P < 0.05$, Dunnett's test).

3) In the older individuals, we observed a significant two-way interaction for day and time-of-day ($F_{19,576} = 1.75, P = 0.03$); there was a significant difference between day 1 and 5 during the first (immediately after awakening) and ninth time point (1 h post-lunch; see Figure 6.1). In the young individuals, we observed a significant two-way interaction for day and time-of-day ($F_{19,925} = 1.65, P = 0.04$); there was a significant difference between day 1 and 5 during the first and second time point (during the first 30 min after the final awakening) and during time points 12, 14, and 15 (early evening).

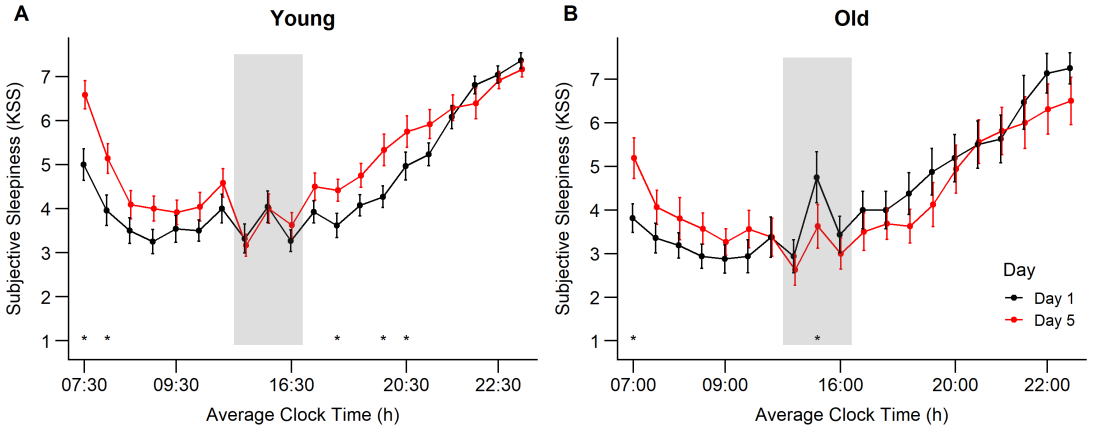

Figure 6.1: Time courses of subjective sleepiness ratings. Displayed are values in young **(A)** and older individuals **(B)** during the first (day 1 , black) and next-to-last day (day 5, red) of the experimental protocol. Data are plotted as a mean for each time point relative to average clock time (h), and the error bars represent the standard error of the mean. * $P < 0.05$, post-hoc comparison between day 1 and day 5, Tukey test. The grey area represent time points with 2-hourly ratings, while the remaining ratings in the mornings and evenings were carried out at 30-min intervals.

3 REM sleep

We reported a change in REM sleep (absolute duration in minutes and percentage TST spent in REM sleep, respectively) across consecutive experimental nights (see chapter 3) and tested further dynamics. We used linear mixed-effects models with a random intercept for the participant, the within-participant factor night-into-the-protocol (6-level factor), the between-participant factor age group (young vs. older), and the interaction between the two factors. One additional model included REM-skip (yes vs. no) as a third factor.

We observed a significant two-way interaction for age and night-into-the-protocol on REM sleep duration in minutes ($F_{5,194} = 2.85, P = 0.02$; see Figure 6.2). In the young individuals, REM sleep increased across four nights with a peak during the fourth laboratory night (BL vs.

fourth night: + 23.33 min, $P < 0.001$, Tukey pairwise testing), exhibited a significant decrease for the fifth night (fourth vs. fifth night: − 16.67 min, $P = 0.003$) and returned to levels of the fourth night during the last laboratory night (BL vs. last night: + 15.81 min, $P = 0.008$). In the older individuals, REM duration was shorter ($F_{1,40} = 7.97, P = 0.007$) but was not affected by the experimental night.

Percentage TST spent in REM sleep was affected by the night-into-the-protocol factor ($F_{5,194} = 6.19, P < 0.001$) and showed a similar dynamic than minutes REM sleep: BL vs. fourth night: + 2.60 % TST REM sleep, $P = 0.005$; fourth vs. fifth night: − 2.41 % TST REM sleep, $P = 0.013$; BL vs. last night: + 2.81 % TST REM sleep, $P = 0.002$.

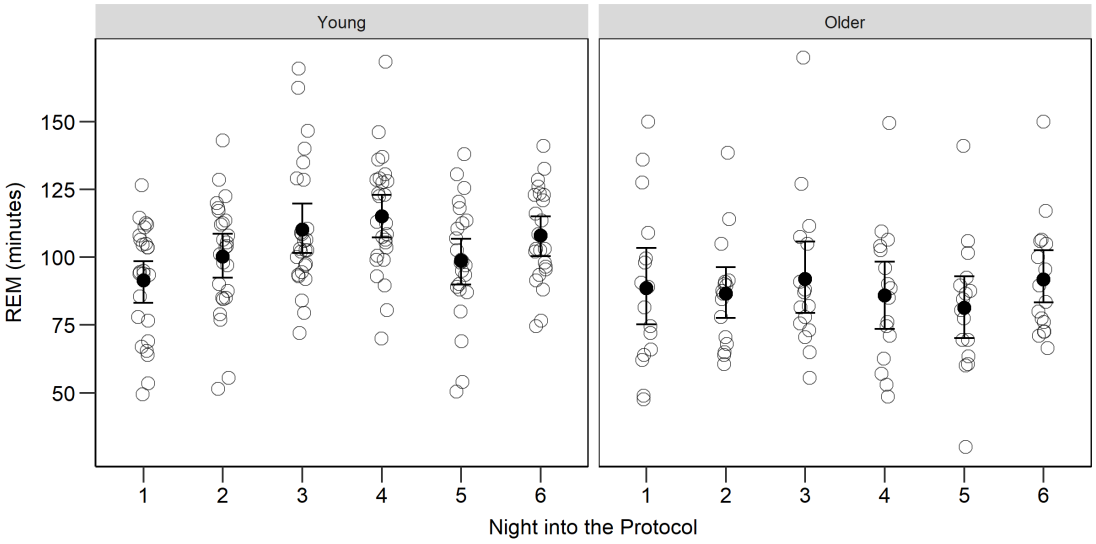

Figure 6.2: REM sleep duration (minutes) over the six consecutive nights of the laboratory experiment. The young are displayed on the left and the older individuals on the right panel side. Open circles represent raw values per night, filled circles represent mean values, and error bars represent 95 % confidence intervals.

REM sleep duration during the first experimental night might have been underestimated. Occasionally, a skipping of the first REM episode is seen: where REM is expected (i. e., after a consolidated period of SWS), only a lightening of the sleep process (i. e., a sleep stage transition to N1 sleep or a brief awakening) occurs, especially during the first night in a new environment (Agnew et al., 1966) or in younger individuals (Jenni & Carskadon, 2004). During all 246 nights, we observed a skipping of the first REM episode in 11 nights: 9 in young individuals (5 in males) and 2 in the older (both in one female); 5 during the first night; mean age in the young individuals was 21.96 years as compared to the mean age of the total young sample of 24.58 years.

In those who skipped the first REM sleep episode, all-night REM sleep duration and % TST spent in REM ($F_{5,207} = 8.04, P = 0.005$) were significantly shorter irrespective of the laboratory night (− 4.46 % TST REM sleep; − 9.68 min; $P < 0.01$, Tukey pairwise testing). Excluding those who skipped the first REM episode, did not affect the observed REM dynamics for REM sleep duration in minutes in the young individuals (BL vs. fourth night: + 24.07 min, $P < 0.001$;

fourth vs. fifth night: − 18.56 min, $P < 0.001$; BL vs. last night: + 15.75 min, $P = 0.013$, all Tukey pairwise testing) and TST spent in REM sleep (BL vs. fourth night: + 2.40 % TST, $P = 0.017$; fourth vs. fifth night: − 2.62 % TST, $P = 0.005$; BL vs. last night: + 2.50 % TST, $P = 0.001$; see Figure 6.3). Consequently, the observed time-in-study effects observed for REM sleep duration cannot be explained by first night effects alone.

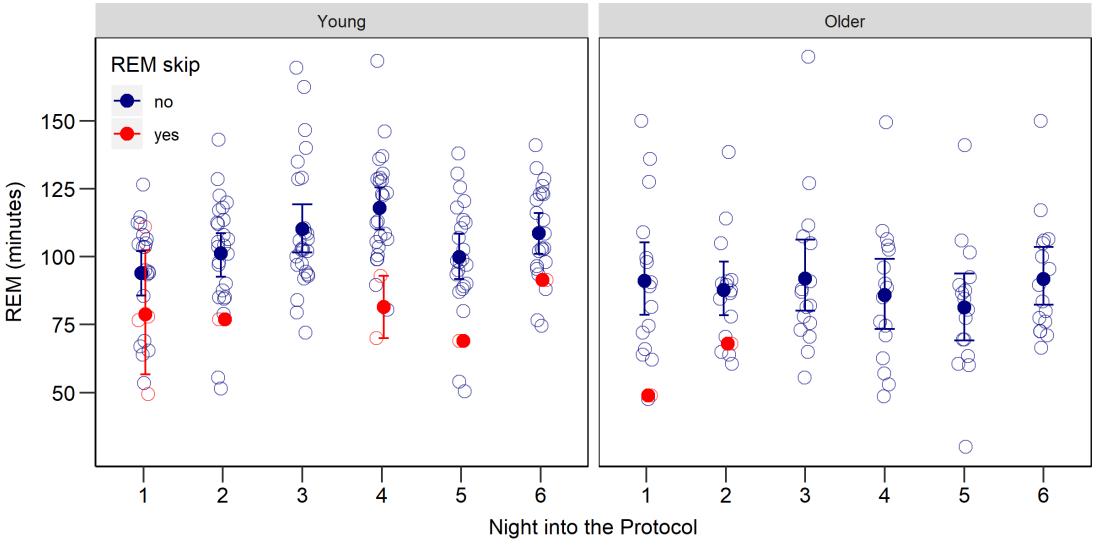

Figure 6.3: REM sleep duration (minutes) over the six consecutive nights of the laboratory experiment. The young are displayed on the left and the older individuals on the right panel side. Those nights where a skipping of the first REM sleep episode was observed are highlighted in red. Open circles represent raw values per night, filled circles represent mean values, and error bars represent 95 % confidence intervals.

4 Noise exposure under field conditions

Within the SiRENE framework, noise exposure in 99 individuals all over Switzerland was recorded in their homes over a period of seven days (Locher et al., 2018). The mean number of identified noise events per individual and night during actimetry-verified sleep times was 26 with a range of 0-257 noise events (unpublished data, Figure 6.4). To illustrate the distribution of maximum SPL in the field, Figure 8 depicts in- and outdoor maximum SPL of single noise events automatically detected from the all-night acoustic recordings of the SiRENE field experiment. To derive indoor values, the SPL, which was recorded outside with a microphone placed on the window of the bedroom, was corrected according to the individual preferred window position as closed, tilted, or open (Locher et al., 2018). This correction resulted in a reduction and a different distribution of indoor compared to outdoor exposure levels. Other field experiments reported median maximum indoor SPL of 44 dB(A) (Basner et al., 2004) or 49 dB(A) (Elmenhorst et al., 2012). Single noise events were not classified according to their sources, but a similar all-night field acoustical recording in Switzerland revealed that the majority of noise events stem from traffic sources and church bells (Brink & Omlin, 2013). A small overlap of maximum SPL

distributions between laboratory and field experiments limits the possibility to transfer results in a 1:1 fashion and thus, to explain long-term health effects of habitual nighttime noise exposure as evidenced by ample epidemiological studies.

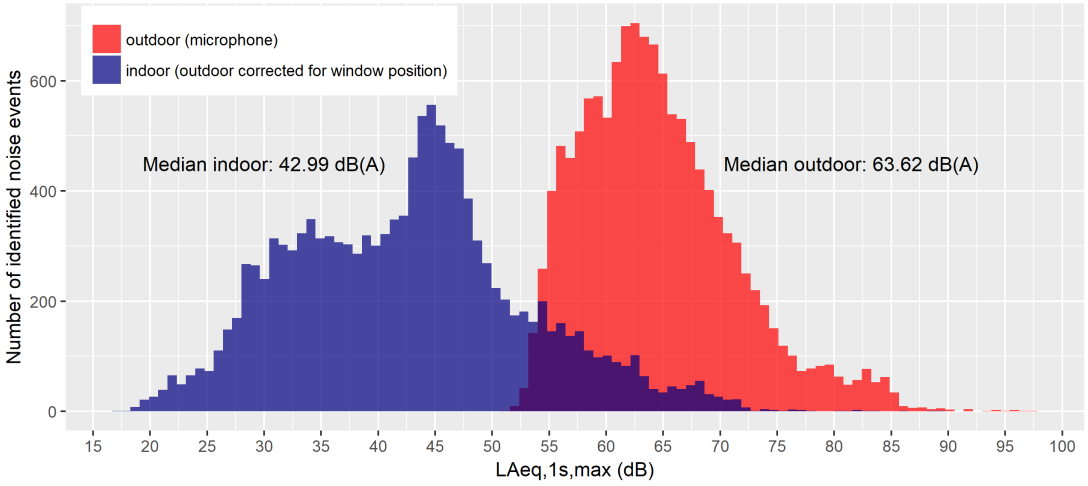

Figure 6.4: Acoustical characteristics of noise events recorded under field conditions. Distribution of the $L_{Aeq,1s,max}$ of 13,147 automatically identified noise events recorded in homes of 99 individuals (i. e., 499 individual nights; events occurred during actimetry-verified sleep times) all over Switzerland (Locher et al., 2018). The outdoor SPL in red was derived from acoustical recordings of an outdoor microphone placed in the middle of the window pane. The indoor SPL in blue was calculated as the difference between the outdoor levels and a correction factor for the respective preferred window position using values from Locher at al. (2018).

Chapter 7

Discussion

The main objective of this thesis was to characterize the effects of nighttime transportation noise and age on sleep microstructure. The main results were:

- *All-night noise effect.* In the older individuals, sleep was more fragmented under noise exposure compared to noise-free nights as indicated by an increase in the number of NREM EEG arousals, the number of awakenings from NREM sleep, the amount of N1 sleep, and the number of total sleep stage changes, while there were no effects on sleep macrostructure and all-night arousal and awakening rates in the young, which were independent of time-in-study effects.
- *More fine-grained analyses on the temporal distribution of EEG arousals both within and across sleep cycles.* EEG arousal rates increased during eventful noise exposure when compared to noise-free nights in both age groups across all NREM sleep episodes; the difference in results between the all-night (see above) and the cycle analyses are discussed in detail in the discussion of Chapter 5. Older participants showed higher overall EEG arousal rates, being higher at the beginning than at the end of each NREM sleep episode in contrast to an opposite pattern in young participants.
- *Different arousal response marker (EEG arousal (CA), awakenings, autonomic arousals (AA), body movements (MOV).* For most arousal response markers, frequency of occurrence critically depended on the age group, while all-night rates showed no effect of transportation noise exposure. While EEG arousal rates were higher in the older than in the young individuals, autonomic arousal and movement rates showed higher rates in the young individuals.
- *Event-related analysis using single railway noise events.* Awakening probability increased with maximum SPL, sleep cycle, and with prior sleep stage N1 when compared to N2 sleep. EEG arousal probability increased with maximum SPL, maximum SPL slope, sleep cycle, older age and was significantly higher from N1 and significantly lower from SWS when compared to N2 sleep.
- *Event-related analysis using both single railway and road noise events (noise scenarios Road C and Rail D).* For all four arousal response markers, the probability of an event-related arousal was significantly higher than spontaneous probabilities with AA reactivity being higher in the young than in the older and CA reactivity being higher in the older compared to the young individuals.

- *Spindle rates.* Spindle rates were stable across nights for the young individuals but decreased during noise nights compared to the noise-free nights for older individuals. In the railway noise event-related analysis, one railway noise event type (among the loudest with a maximum SPL of 60.8 dB and with the highest maxSPLslope of 5.2 dB/s) caused a significant reduction in spindle rates in both age groups.
- *Spindle amplitude.* Spindle amplitude showed consistently significant differences between the pooled noise-free and the pooled noise nights in both age groups: maximum spindle amplitude was significantly reduced during exposure of noise scenarios Road A and B. In the railway noise event-related analysis, maximum spindle amplitude was significantly reduced during exposure compared to non-exposure periods in both age groups, which was not related to any acoustical characteristic of the single noise event.
- *Time-in-study effect.* Time-in-study effects were observed for REM-related variables with a decrease in REM onset latency, an increase in the number of NREM-REM transitions and the duration of REM arousals as well as an increase in N1 sleep onset latency throughout the protocol for both age groups. Additionally, the young subgroup showed an increase in REM sleep duration (at the expense of N2 sleep, which decreased in duration), in the duration of NREM arousals, and latency to N2 sleep over the course of the six-night protocol. In the older group, we observed a decrease in TST, SE, and N2 sleep duration and an increase in the number of sleep stage changes between the first and the last experimental night.

The following discussion is divided in three parts. First, observed age and noise effects will be discussed and it will be outlined how our data contribute to the understanding of transportation noise effects on sleep. Second, some ideas regarding the difference in results for the polysomnographical evaluation of sleep (objective) and the subjective evaluation of sleep in our experiment will be discussed. In a last step, some limitations of the present experiment will be outlined and some ideas for future avenues in the field of noise research will be provided.

1 Age and noise effects on sleep

With aging, sleep undergoes alterations in duration, initiation, and maintenance (Mander, Winer, & Walker, 2017). Amounts of intra-sleep wakefulness, N1, and N2 increase, while amounts of SWS and REM sleep as well as total sleep time (TST) and sleep efficiency (SE) decrease with aging (Ohayon et al., 2004). Furthermore, transient activation also increase with aging and are part of the normal aging process in humans (Bonnet & Arand, 2007; Boselli et al., 1998; Klerman et al., 2013; Terzano et al., 2002; Yetton et al., 2018), while sleep spindles undergo a marked decline with aging (Carrier et al., 2001; Landolt et al., 1996; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Purcell et al., 2017; Schwarz et al., 2017; Warby et al., 2014). Because of the age-related alterations in sleep macro- and microstructure as well as the higher self-reported noise sensitivity in older than in young individuals (Matsumura & Rylander, 1991; Schreckenberg et al., 2010), older individuals are generally considered at risk for nighttime noise effects on sleep (Basner & McGuire, 2018; Muzet, 2007). The age-related decline in gray and

white matter (as outlined in Chapter 1) as well as other neurophysiological and neurochemical changes in older individuals brains might underlie the prominent changes in sleep with advancing age (Mander, Winer, & Walker, 2017). Inter-individual and age-specific differences in sleep-related oscillations and transient events also depend on the structural configuration and integrity of the underlying neural network (Mander, Zhu, et al., 2017; Piantoni et al., 2013).

We observed the normal expected sleep changes with aging (see Supplementary tables in Chapter 3). In addition, sleep was more fragmented under noise exposure compared to noise-free nights as indicated by an increase in the number of NREM EEG arousals (+ 1.21 n/h TST), the number of awakenings from NREM sleep (+ 0.39 n/h TST), the amount of N1 sleep (+ 5.21 min), and the number of total sleep stage changes (+ 1.85 n/h TST) in the older individuals, while we observed no changes in sleep micro- and macrostructure in the global analysis for the young individuals. Typically, laboratory noise experiments were conducted in young individuals (Griefahn et al., 2006; Smith et al., 2017) The two experiments that included a wider age range did not observe differences in noise effects on sleep macro- and macrostructure between young (mean age of 25.8 years) and middle-aged (mean age of 52.2 years) individuals (Saremi et al., 2008) or did not analyse data accordingly (Basner et al., 2011).

The main aim of the first paper (Chapter 3) was to evaluate the role of sleep spindles, spontaneous NREM sleep-related brain oscillations, for protecting sleep in the presence of transportation noise exposure. It has been hypothesized that cell firing during spindles gates afferent signaling to the cortex (Steriade, 2006) in order to isolate the cortex from environmental throughput and prevent cortical arousal. The basic idea of this proposed biological sleep protection: higher sleep spindle rates (i. e., length of the disconnection between primary sensory cortices and higher-order cortical areas) result in higher sleep stability as processing of sensory stimuli is inhibited as demonstrated in a sample of young individuals exposed to variety of common hospital-recorded noise events (Dang-Vu et al., 2010). As sleep spindle rates undergo a marked decline with aging (Carrier et al., 2001; Landolt et al., 1996; Mander, Winer, & Walker, 2017; N. Martin et al., 2013; Purcell et al., 2017; Schwarz et al., 2017; Warby et al., 2014), inter-individual differences in sleep spindle rates might also implicated in the higher vulnerability to nighttime noise observed in the older individuals in our experiment.

Contrary to our hypotheses, spindle activity was neither related to differences in sleep structure or continuity in noise exposure nights nor was it a significant predictor for cortical activation probabilities from single railway noise events. And, cortical activation probability that increased throughout the night was not related to naturally occurring variations in spindle rate over successive NREM sleep cycles. If spindles are sleep-protective, cycle-specific intra-night variability in spindle rates should affect arousal probabilities, both event-related and spontaneous. But, the linear increase in spindle rates across successive NREM cycles in the young was accompanied by an increase rather than a decrease in arousal probability from single railway noise events. Spindle amplitude was consistently decreased during noise compared to noise-free nights across all EEG derivations and age groups, both in the all-night analyses and during selected intervals of noise exposure compared to non-exposure in the event-related analysis and might be interpreted as a disruption of synchronization of TC oscillation (Weigenand

et al., 2016). In conclusion, we did not find an independent effect of spindles on a variety of sleep structure and continuity markers of noise disturbed sleep after controlling for age. Sleep spindles are trait-like transitory EEG oscillations, that may reflect stable sleep but do not necessarily protect the sleeper against external stimuli such as nighttime transportation noise. The first notion of an association between sleep quality and spindle activity stems from experiments on drug-induced changes on sleep: the intake of flurazepam, a benzodiazepine used to treat sleep disorders, caused a marked increase in sleep spindle rates as well as in sleep continuity with a decrease in N2 sleep latency, N1 sleep duration, and awakening rates (Johnson, Hanson, & Bickford, 1976). Although sleep was more sound, this had no effect on the arousal threshold, which was unaffected by the spindle rate (Church et al., 1978). Experiments in individuals suffering from insomnia, the ongoing subjective experience of difficulty initiating or maintaining sleep, early-morning awakening, or chronic experience of non-restorative sleep, despite sufficient sleep opportunities (Edinger et al., 2004), add to the sleep spindle controversy. If sleep spindles protect sleep, the hypothesis of decreased spindle activity in insomnia would be legitimate. However, patients with insomnia do not differ from healthy controls in spindle activity (Weiner & Dang-Vu, 2016), as shown for absolute NREM sigma power between primary insomniacs and healthy controls (Bastien, LeBlanc, Carrier, & Morin, 2003; Buysse et al., 2008; Y. M. Wu et al., 2013) as well as in all-night spindle rates between patients that suffer from chronic primary insomnia and good healthy sleepers (Bastien2009).

Cortical arousals are not distributed randomly, but tend to cluster around certain time points during sleep (Halasz et al., 2004; Terzano & Parrino, 2000; Terzano et al., 2000). Thus, we used a more sophisticated approach that controlled for within- and across sleep cycle effects in a next step to characterize the observed increase in sleep fragmentation in the older individuals further (Chapter 4). Arousal rates were higher during the eventful noise exposure compared to the noise-free condition (+ 0.1 n/CSD with a standardized length of 6.9 min), independent of the age group, meaning that arousal rates did not further increase upon noise exposure with aging. However, strong age effects were observed for the overall level and the shape of the arousal rate time course: in the older group, arousal rates tended to be higher at the beginning of the cycle compared to its end, while in the young group, arousal rates at the end of the cycle were consistently higher than at the beginning of the cycle. It might be speculated that increased EEG arousal rates at the beginning of a cycle reflect an impaired sleep deepening process when sleep states switch to NREM sleep, either from wakefulness during the sleep onset period or from REM sleep for subsequent sleep cycles. The general increase in EEG arousal with advancing age might be due to the decreased ability to maintain consistent and stable sleep states with aging (Conte et al., 2014; Klerman et al., 2013). Per definition, sleep macro- and microstructure parameters are interrelated: for example, the occurrence of EEG arousals result in a sleep stage change to lighter sleep, usually from N2 to N1 sleep or from REM sleep to N1 sleep (Berry et al., 2016; Bonnet et al., 1992). The absence of a consistent N1 sleep effect and the increase in arousal rates, depending on the type of analysis, might indicate that sleep deepened quickly again after arousal onset and therefore not affecting global macrostructure parameter such as amount of N1 sleep. Others reported no (Dang-Vu et al., 2010; Saremi et al., 2008; Smith et

al., 2017) or only mild increases in N1 sleep (+ 4 min Basner et al., 2011). Post-arousal sleep dynamics might be related to habituation (i. e., lower response rates with the repeated exposure of noise events). However, quick post-arousal sleep deepening or the overall absence of an arousal response to single noise events might also be the result of a cumulative increase in sleep pressure due to increasing sleep disruption over several nights of noise exposure as during our study design (see also Bonnet, 1985; Chugh et al., 1996; Stepanski, Lamphere, Roehrs, Zorick, & Roth, 1987).

Finally, we analysed whether other arousal response marker, such as AA or MOV were affected by noise exposure (Chapter 5). There was no effect on arousal response incidence during noise exposure nights, but AA occurred more frequently in the young than in the older and CA were more numerous than AA in the older individuals. This finding is surprising as AA were considered a very sensitive marker for arousal responses to auditory stimulation during sleep (Catcheside et al., 2002; Davies et al., 1993; Pitson et al., 1994). The observed age-dependent modulation of the frequency of occurrence of the arousal response might reflect age-related changes in autonomic nervous system functions as discussed in detail in Chapter 5. Whether magnitude rather than frequency of occurrence of the cardiac arousal response constitutes cardiovascular burden of arousal responses during sleep will require future investigation.

The all-night arousal rates were not consistently increased with noise exposure, but event-related arousal probabilities (for AA and CA) were significantly higher during the two eventful noise exposure nights than the spontaneous probabilities determined from the first noise-free night. Clustering of arousal responses around single noise events in the absence of additional reactions (i. e., all-night rates were stable) suggest a redistribution of arousal responses that only replace spontaneous arousal on the absolute all-night level. This argument was first put forward by Muzet et al. (1974) who observed that approximately 50 % of all-night body movements, during both NREM and REM, occurred in proximity of 80-92-dB tone pulses in the absence of an all-night increase in body movements during noise exposure nights. Similarly, Basner et al. (2011) reported that a fair amount of event-related activation reactions replaced spontaneously occurring ones: up to 93 % for awakenings and up to 67 % for EEG arousals. However, to evaluate the significance of additional or replaced arousal reactions it is crucial when they occur. Sleep follows a characteristic within-cycle dynamic with an u-shaped time course suggesting that both the beginning and end of NREM sleep cycles are phases of reduced physiological sleep stability. Noise exposure did not affect the shape of the EEG arousal time course suggesting that eventful noise exposure leads to an unspecific increase of EEG arousals that was embedded within the physiological structure of sleep stability during the night.

Conclusion

The observed small effects of noise exposure on sleep might raise the question whether the level of noise exposure was too low. However, the level of noise exposure depends on the question. The overall aim of the SNF-project (SiRENE) was to combine experimental and epidemiological research to investigate acute, short- and long-term noise effects on sleep and cardiometabolic outcomes so that we chose a moderate level of noise exposure of $L_{Aeq,1h}$ of 45 dB at the ear of

the sleeper (with maximum SPL for single noise events between 50.1 and 61.7 dB; all starting from a background level of 30 dB)–a noise level people are exposed to under real-life conditions during the nighttime in Switzerland (Héritier et al., 2018).

Pre-specified bedtimes might result in an overestimation of noise-induced effects on sleep onset latencies as individuals with a later circadian preference might have more difficulties falling asleep than individuals with an earlier circadian preference when bedtimes are fixed as in most noise experiments at 23:00 h. Advancing the sleep episode due to experimental obligations might phase advance the circadian system and impact on REM sleep which is under strong circadian control: a phenomenon that might have happened in a consecutive 11-day laboratory study where an increase in amount of REM sleep and a decrease in REM latency over the course of the experiment was found (Basner et al., 2011). But, we also observed an increase in REM sleep duration over the course of our six-night laboratory stay and controlled for habitual bedtimes (i. e., bedtimes within $\pm$ 30 min of habitual bedtime). Not only SWS but also REM sleep is under homeostatic control, meaning that SWS and REM sleep pressure increase during wakefulness but also during times spent in the opposing sleep stage (Franken, 2002). Assuming that most individuals were partially sleep deprived under habitual conditions, sleep saturation prior to the laboratory experiment with the demand for an 8-h night sleep might have resulted in a recovery for SWS sleep pressure but was incomplete for REM sleep. However, there are additional factors that influence REM sleep, such as seasonal variations or light exposure history. During winter, REM sleep duration increased ($+$ 27.9 min) at the expense of SWS duration that decreased ($-$ 6.6 min) when compared to summer as assessed under laboratory conditions (Kohsaka, Fukuda, Honma, Honma, & Morita, 1992); however, it must be noted that percentage REM sleep was not significantly different as TST also increased during winter. In a similar vein, it was demonstrated that REM sleep duration depended on preceding daytime light exposure: higher maximal intensity of light was associated with lower amounts of REM sleep (Wams et al., 2017). It is possible that the light exposure situation during the six-day laboratory stay with daytime levels as low as 500 lux resulted in a gradual increase in time spent in REM sleep, especially in those who participated during summer and had a different history of bright light exposure than those who participated during the winter months.

We are far from belittling the effects of transportation noise on sleep. Strong and ample evidence from epidemiological research on the relationship between long-term residential noise exposure during the nighttime and adverse health outcomes contradicts marginal acute and short-term effects usually observed in laboratory settings where generally very healthy individuals were included. However, even mild acute or short-term effects might add up under chronic exposure, given that environmental noise exposure is persistent over time and affects millions of people (Foraster et al., 2017). Long-term noise effects might be the result of accumulated reactions to single noise events over time that have an additive or synergistic effect on a chronically dysregulated stress system that, in turn, increases the risk for negative long-term health outcomes (Münzel et al., 2017; Recio et al., 2016). Most evidence was accumulated for the link between long-term residential transportation noise exposure and the cardiometabolic system (Münzel et al., 2014) including established risk factors for cardiovascular disease (CVD),

as for example obesity (Christensen et al., 2016; Pyko et al., 2017), hypertension (Jarup et al., 2008; van Kempen & Babisch, 2012), vascular health (Foraster et al., 2017), hyperglycemia (Eze, Imboden, et al., 2017), or type-2 diabetes (Clark et al., 2017; Eze, Foraster, et al., 2017; Sørensen et al., 2013) as well as established CVD, such as ischemic heart disease (Héritier et al., 2017; Vienneau, Schindler, Perez, Probst-Hensch, & Röösli, 2015) or heart failure (Héritier et al., 2017; Sørensen et al., 2017)–supporting the view of nighttime noise as a cardiovascular risk factor (Münzel et al., 2014). In the most severe case, it may well be, that a single noise event exposed to a susceptible organism triggers the most adverse outcome, as for example myocardial infarction and unexpected premature death (Recio et al., 2016).

Consequently, we rather want to turn the attention to the remarkable ability of the sleeping brain to adapt to nighttime noise, at least as demonstrated for our noise exposure of $L_{Aeq,1h}$ 45 dB with maximum SPL between 50.1 and 61.7 dB. Under very controlled laboratory conditions, healthy young and older individuals were surprisingly able to adapt to the stress imposed by four nights of transportation noise exposure: additional arousal primarily occurred during physiological phases of fragile sleep and this did not impact systematically on all-night sleep macrostructure. The healthy human brain exerts powerful *guardians of sleep*, "sentinals of a restorative night" (Parrino & Vaudano, 2018, p. 100). This includes the three core processes (the homeostatic, the circadian, and the ultradian processes), sleep microstructural elements, i. e., arousal, KC and delta bursts, sleep spindles, and CAP–all integral elements of sleep regulation as well as sleep-related behavior and cognition, such as dreaming (Parrino & Vaudano, 2018). The view of a noise-resilient sleeping brain is supported by experiments that used even higher maximum SPL than in our experiment: SWS was not reduced as compared to quiet conditions for continuous 93 dB white noise exposure (Scott, 1972), 90 phon intermittent white noise exposure (Okuma & Honda, 1978), or 95-100-dB tone pulses with inter-stimulus intervals ranging between 1-80 s (Nakagawa, 1987) in male, healthy college students aged between 18 and 27 years. And, 24-h exposure to tone pulses of 80, 85, or 90 dB during a period of 30 days in young men, resulted in a reduction of percentage spent in SWS in the 90-dB condition only (Townsend et al., 1973). This guardians of sleep might have provided a low-cost adaptation to ecologically valid transportation noise exposure and might have played exceptionally well under conditions of exemplary sleep hygiene as in our experimental protocol. Controlled conditions comprised sleep duration (constant 8-h sleep opportunity in the laboratory and the week prior to the experiment that made chronic partial sleep deprivation less likely), timing of bed and rise times (regular at habitual bed and rise times during approx. two weeks, during the laboratory part and the week prior to that), food and liquor intake (regular feeding times with a strict nighttime fast of 13 hours, no alcohol or caffeinated beverages), light exposure levels (constant daytime light levels of 500 lux, without significant evening blue light exposure of smartphones, computers, or tablets), and sleep environment (constant temperature and humidity levels, no additional noises from bed partners or additional community noise). Nevertheless, we have evidence from sleep, cardiometabolic, and stress parameters that adaptation challenged the system and caused its price anyway. We observed an increase in sleep onset latency in both age groups (to N1 in both and to N2 only in the young group) and a decrease in sleep efficiency, N2

sleep duration as well as an increase in the number of sleep stage changes in the older group across the six laboratory nights (Rudzik et al., 2018). In addition, we observed increased glucose and insulin levels in the mornings after four nights of noise exposure (Thiesse et al., 2018) as well as an increase in mean AA duration during railway noise exposure nights and an increase in evening cortisol levels after eventful road noise exposure nights (Thiesse et al., 2019), all compared to baseline conditions. Whether this is due to the laboratory conditions per se or the noise exposure cannot be clearly disentangled. It is to be expected, however, that guardians of sleep might be outplayed by dysregulation of stress systems, high allostatic load or overload (Karatsoreos & McEwen, 2011) imposed on human physiology by characteristic lifestyle factors in modern society (i. e., chronic sleep deprivation, high social stress, overfed, low physical activity, circadian misalignment or rhythm desynchrony, etc.) making the organisms more vulnerable and giving rise to detrimental effects of long-term nighttime noise exposure on health as evidenced by a substantial body of epidemiological results.

2 Subjective evaluations

The objective assessment of sleep quality using PSG demonstrated only mild effects of transportation noise exposure on sleep in our experiment, which is in line with the results of other experiments (Basner et al., 2011), while the psychological experience of sleep was more affected. Noise exposure was perceived as annoying, irrespective of age: annoyance was significantly higher for all noise exposure nights (for pooled exposure as well as on the individual noise contrast levels) compared to the noise-free nights. Noise exposure reduced global subjective sleep quality irrespective of age. Moreover, the young individuals experienced an increase in number of remembered awakenings and the older reported a decrease in subjective TST–both parameter indicating a subjective disruption of sleep continuity by noise exposure. Both age groups reported on higher subjective sleepiness in the mornings after noise exposure nights: this continued until 30 minutes after the final-awakening in the older individuals and until 120 minutes in the young individuals.

The psychological construct *subjective sleep quality* is considered a “complex phenomenon that is difficult to define and measure objectively” (Buysse et al., 1989, p. 194) and several attitudes, perceptions, judgements, and information might be used to devise the subjective evaluation of good or poor sleep. Using a qualitative approach, it was demonstrated that non-sleep disturbed individuals evaluate the quality of their sleep to a large extent according to evaluations of emotional and cognitive daytime functioning, namely the subjective sleepiness upon waking and during the day and the subjective feeling of being rested and restored upon waking (Harvey, Stinson, Whitaker, Moskovitz, & Virk, 2008). The continuity of sleep was one of the main PSG-verified sleep measures that was related to the subjective evaluation of sleep as demonstrated for number of remembered awakenings (Harvey et al., 2008) and sleep efficiency, the TST during time in bed (Akerstedt, Hume, Minors, & Waterhouse, 1994; Saletu, 1975). In addition, validated sleep quality instruments also include judgements about the quality

and length of the sleep onset period (Parrott & Hindmarch, 1978) or about the necessity of sleep medication intake (Buysse et al., 1989).

We have two hypotheses regarding the difference in results for polysomnographical evaluation of sleep (objective) and the subjective evaluation of sleep in our experiment.

First, it is possible that sleep was not disturbed objectively by noise exposure and only the subjective evaluation of it was biased. The subjective evaluation of poor sleep might be the result of the expectation or belief that nighttime noise exposure will impair sleep quality. The role of behaviors, beliefs, interpretations, and maladaptive mental processes, such as worrying about sleep, fear of sleep deficits, or unrealistic expectations about sleep for the development of sleep difficulties (Belanger, Savard, & Morin, 2006) was primarily investigated in insomniac patients. The belief of the sleep-disturbing potential of noise might result in an increased monitoring of the sleep behavior resulting in the subjective experience of increased number of awakenings or less time spent asleep as observed in our experiment. In the literature, vigilant monitoring behaviour (i. e., watchfulness) was conceptualized using a preferential information processing style during wakefulness, a complex psychological coping style, called Monitoring/Blunting (Voss, 2001). Faced with uncertain or potentially dangerous situations, Monitors have a high need to seek information, while Blunters tend to avoid information seeking and prefer deflective behavior under these circumstances. Faced with an unsafe sleep environment (i. e., sleep in an unfamiliar environment, sleep disruption using auditory stimulation, or anticipation of a potentially stressful social situation), sleep of Blunters was more interrupted (i. e., lower sleep efficiency, more sleep stage changes and longer intra-sleep wakefulness) and less deep (i. e., spent less time in SWS) than sleep of Monitors (Voss, 2001). Blunters were also more likely to have primary insomnia (Voss, Kolling, & Heidenreich, 2006). In the same vein, insomnia might be adaptive under circumstances of perceived threat (Nunn, Samson, & Krystal, 2016). It is very likely that differences in neural network architecture and activity that underlie personality, character, or strong behavioural preference also influence the way we sleep and perceive sleep as sleep. To complicate things further, the evaluation of being asleep can differ between individuals, a phenomenon known as “sleep state misperception”, especially seen in insomniac patients, i.e. the underestimation of TST–when compared to PSG-derived TST–due to ongoing mental activity, such as thoughts or rumination (Manconi et al., 2010). How expectations also influence the evaluation of day-time functioning was demonstrated in a sample of insomnia patients provided with sham feedback about their actimetry-verified sleep quality: those provided with a negative feedback about sleep quality during the subsequent night, irrespective of their actual sleep quality, reported higher levels of sleepiness during the consecutive days compared to those provided with positive feedback (Gavriloff et al., 2018). The expectation of poor sleep in the presence of nighttime noise might result in the increased subjective sleepiness during the first 2 h after final awakening in the young individuals in our experiment.

Other psychological processes might play a role when evaluating the effects of noise on sleep as illustrated in the following small case example (inspired from Brink et al., 2008):

> Imagine: it is six in the morning, operating hours of the nearby Zurich Airport just started, you woke up and in the distance an aircraft takeoff sound is still slightly perceivable. You attribute your awakening to the starting jet and immediately you get very angry: you have a distressing day ahead of you, you need your sleep and now you woke up from a jet full of tourists?! Life is just unfair you think, why me...? You are getting up because you know that in the end, you won't be able to get back to sleep, at least for today.

Assume, the starting jet in the above example just coincided by chance with a physiological awakening. But, post-awakening sleep onset (PASO) is delayed, which occurs usually after 30-60 seconds for brief awakenings, at least in young individuals (Goldenberg et al., 1981; Vallat et al., 2017). When PASO is delayed, the chance of resuming full external and/or self-awareness is high, so that the noise event is perceived consciously and is used to attribute the awakening to. Additionally, emerging anger or the feeling of helplessness might activate the organism and prolong PASO further or, as in the extreme case of the example, PASO might not be possible at all so that the entire sleep episode is terminated. Consequently, one effect of noise on sleep could be to prolong physiological awakening reactions and, in turn, the number of next-morning remembered awakenings, which depend on the duration of the awakening (Vallat et al., 2017), without necessarily increasing the actual all-night number of awakenings. Thus, it has been speculated that the conscious perception of single noise events might influence the subjective evaluation of sleep quality and noise annoyance (Basner et al., 2011; Basner, Müller, et al., 2008), i. e., the lower the number of noise events, the lower the probability of a subjective sleep quality impairment. In our experiment, the total number of railway noise events was 80 (Rail D) as compared to 400 events in the high eventful road noise scenario (Road C), while Road A and B were characterized by continuous noise (i. e., without noticeable single noise events). The global subjective sleep quality decrease as well the decrease in subjective TST were observed for the road noise scenarios with a high number of single noise events or continuous noise exposure. Similarly, Basner et al. (2011) showed more subjective effects for noise exposure nights with 80 and 120 single noise events than for nights with 40 single noise events. We cannot conclude that road noise is more detrimental or annoying than railway noise as we did not balance for the number of noise events or maximum SPL in our experimental protocol: the constant $L_{Aeq,1h}$ of 45 dB for the different noise scenarios and the large difference in number of single noise events necessarily imply that the SPL progress very differently between a single road and railway noise event (see Figure 1.5 for an illustration).

It is highly speculative, but negative noise-related attitudes might impact on sleep-related basic attentional processes influencing selective auditory information processing or autonomous nervous system reactions that further arouse the sleeper or delay PASO. For example, the negative attitude towards church bell ringing was associated with a higher awakening probability from single church bell events (Brink, Omlin, Müller, Pieren, & Basner, 2011). The relationship between negative attitudes towards specific noise sources and sleep was further demonstrated in a sample of 81 residents living in the vicinity of Frankfurt Airport: individuals with a negative

attitude towards air traffic had a longer sleep onset latency, longer intra-night wakefulness duration, less deep sleep and sleep efficiency than individuals with a moderate or positive attitude (Elmenhorst et al., 2017). Other attitudes and beliefs might play a role in mediating or moderating the effects of physical sound on specific noise effects: noise annoyance, i. e. the "long-term dissatisfaction, disturbance, or bother with respect to the acoustic environment" (Guski, 1999, p. 45), the evaluation of the noise source in terms of necessity or importance, the trust in source authorities, the environmental political orientation or the fear of harm from the noise source (Brink, Rometsch, Wirth, & Schierz, 2007; Fields, 1992; Guski, 1999).

The other view on the difference in results for polysomnographical evaluation of sleep (objective) and the subjective evaluation of sleep is that objective assessment of sleep was deficient and the subjective evaluation of it was actually correct. Sleep is not an all-or-nothing phenomenon and wake-like and sleep-like EEG oscillations can occur at the same time. For example, cortical activations were demonstrated to occur locally: while recordings within the motor cortex showed wake-like, fast activity, recordings from frontal brain areas indicated clear signs of sleep (Nobili et al., 2011). It is possible, that significant arousal responses were overlooked when using the traditional EEG setup with recordings from the scalp when compared to intracranial recordings. One way of looking at it would be the use of high-density EEG recordings (hdEEG) facilitating higher spatial specificity and the identification of cortical and subcortical generators of EEG activity. Using hdEEG in insomniac patients, Riedner et al. (2016) observed higher alpha activity during SWS in sensory areas (including visual, auditory, and somatosensory parts) compared to healthy controls, which might be interpreted as an ongoing connection with the environment in insomniac patients. However, whether insomniacs have a higher need for a safe sleep environment and therefore process outside information during sleep or the ongoing wake-like activity in those areas constitutes the subjective experience of disturbed sleep cannot be concluded from these data. It is possible that local sleep-wake dysregulations during noise exposure nights, which we were unaware of due to the low spatial resolution of the 12-electrode setup, resulted in the subjective evaluation of disturbed sleep in our experiment.

3 Limitations

The most important limiting factor of our experiment might be a strong self-selection of participants. It is possible that we included a subset of very resilient and noise-resistant individuals. On average, individuals reported rather low levels on the Noise Sensitivity Questionnaire (NoiSeQ), a validated questionnaire to assess noise sensitivity of individuals in different living environments (Schütte et al., 2007). Inclusion in the experiment was not decided upon noise sensitivity values, but the range of possible NoiSeQ values (scale 0-3) was still rather broad with values between 0.34 and 2.10 (mean values in the young and older groups: 1.23 and 1.59). Moreover, most individuals included in our sample did not report on nighttime noise exposure in their habitual residential environment. Overall, we included very healthy young and older individuals who were free of any sleep-related disorders or mental health problems, factors that are generally considered putting individuals at risk for long-term detrimental health effects of

habitual residential noise exposure; as well as children and shift workers (Basner & McGuire, 2018; Hume et al., 2012; Muzet, 2007; Stansfeld, 1992; van Kamp & Davies, 2013; WHO, 2009). In addition, it is reasonable to assume that all individuals with pre-existing chronic somatic disorders, such as type-2 diabetes (Barone & Menna-Barreto, 2011), are at risk. On the other hand, including very healthy individuals in noise experiments is considered standard and laboratory conditions are somewhat extreme noise exposure conditions with typically higher SPL ranges used for playback than measured under real-life conditions in the field (see Chapter *Additional results*, Figure 6.4).

Another factor that complicated the interpretation of results was the experimental design scheduling the two noise-free nights as first and last nights of the protocol: a decision that was mainly influenced by the needs of the glucose tolerance tests scheduled in the mornings after the noise-free nights (nights 1 and 6) and after four nights of noise exposure (night 5). We observed several time-in-study effects, particularly for REM sleep and sleep onset latencies that severely complicated the disentanglement of genuine noise and laboratory effects. Another 11-night laboratory experiment on noise effects on sleep reported similar sleep changes over the course of their protocol (Basner et al., 2011). Laboratory effects might be due to changes in circadian timing as a result of the modified light exposure (overall light levels as well as the difference between artificial and sunlight exposure), changes in physical activity, or psychological factors (social isolation due to laboratory "confinement"; even though participants were always in contact with staff and were encouraged to socially interact).

Another factor was the reliance on visual examination of EEG signals to classify sleep stages and EEG responses as cortical arousal or awakenings. It was demonstrated that the acquisition and interpretation of the quite arbitrary ASDA scoring criteria for manual evaluation resulted in considerable variability and low agreement between different human scorers (Bonnet & Arand, 2007; Drinnan et al., 1998). On the other hand, manual scoring is still considered as gold standard in the field. Sleep staging and EEG arousal scoring was conducted by four experienced raters in our laboratory blind to the respective noise condition; inter-rater accordance was assured $> 85\,\%$. One scorer analyzed all six nights of one participant and the number of scored files was balanced according to the participant's sex and age. Scorers had regular scoring sessions to discuss questionable epochs and align local scoring procedures.

4 Outlook

Future research directions to investigate the effects of nighttime noise on sleep may take advantage of recent methodological, technological, and conceptual developments and ideas.

To reduce the subjective burden of laboratory studies such as ours and provide longer noise exposure instead of an only four-day noise snippet, biometric data might be recorded in the field and combined with habitual noise exposure information as proposed by Münzel et al. (2017). Instead of keeping the plethora of factors that influence sleep, such as lighting levels, physical exercise, caffeine intake, or sleep history constant, all those factors might also be recorded and statistically controlled for in a big enough data set.

Excellent other experiments investigating the effects of transportation noise on sleep, conducted under strict laboratory conditions, are available so that a pooling of different data sets, using a broader variety of different noise stimuli, noise exposure situations, age ranges, and health conditions might be a fruitful avenue. Not only for a meta-analysis (Basner & McGuire, 2018) but also for primary data analysis using the same analysis techniques as recently demonstrated for three big data sets from two German laboratories (Elmenhorst et al., 2019). It might be worth the effort, even though sharing and preparing data always comes at the expense of technical, logistical, and organizational challenges (Redline, Dean, & Sanders, 2013).

In general, resilience is considered as "the capacity and dynamic process of adaptively overcoming stress and adversity while maintaining normal psychological and physical functioning" (G. Wu et al., 2013, p. 1) and this successful adaptation to stress and adversity is the result of manifold genetic, epigenetic, developmental, psychological, and neurochemical mechanisms (G. Wu et al., 2013). Whether day-time resilience translates to an increased ability to deal with the stress imposed on the organism by environmental noise during sleep has not been investigated in detail. But it is likely that neural correlates of psychological characteristics that promote resilience are also linked to sleep (Parrino & Vaudano, 2018). Low and high resilient, otherwise healthy individuals might be included to test the hypothesis whether less resilient individuals are more vulnerable to noise-induced sleep disruptions.

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Abbreviations

AA	Autonomic arousal
AASM	American Academy of Sleep Medicine
AIC	Akaike information criterion
ARAS	Ascending reticular activating system
ASDA	American Sleep Disorders Association
AWR	Awakening
BDI	Beck Depression Inventory
BIC	Bayesian information criterion
BL	Baseline night
BOLD	Blood oxygenation level dependent
CA	Cortical arousal
CAP	cyclic alternating pattern
CSD	Cycle subdivision
CVD	Cardiovascular disease
EEG	Electroencephalography
ECG	Electrocardiogram
EMG	Electromyogram
EOG	Electrooculogram
ERP	Event-related electrical potential
ESS	Epworth Sleepiness Scale
fMRI	Functional magnetic resonance imaging
GAMM	Generalized additive mixed model
GLMM	Generalized linear mixed model
HPA	Hypothalamic-pituitary-adrenocortical axis
HR	Heart rate
HRV	Heart rate variability
IR	Intermittency ratio
KC	K-complex
LEF-K	Lärmempfindlichkeitsfragebogen
MaxSPLslope	Maximum slope of the sound pressure level
MCTQ	Munich Chronotype Questionnaire
MOV	Body movement
MSF_{sc}	Mid-sleep on freedays corrected for sleep duration
NF	Noise-free
NoiSeQ	Noise Sensitivity Questionnaire
NR	NREM-to-REM transition
NREM	Non-rapid eye movement sleep
NTP	Neuronal transition probability model
N1	Stage 1 NREM sleep
N2	Stage 2 NREM sleep
OSAS	Obstructive sleep apnea syndrome

PASO	Post-awakening sleep onset
PAT	Phases d'activation transitoire
PLMD	Periodic limb movement disorder
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RC	Recovery night
REM	Rapid eye movement sleep
RMS	Root mean square
RNE	Railway noise event
RT	Reticular thalamic nucleus
SAM	Sympatho-adrenal-medular axis
SE	Sleep efficiency
SEL	Sound exposure level
SO	Slow oscillations
SPL	Sound pressure level
STAI	State-Trait Anxiety Inventory
SWA	Slow-wave activity
SWS	Slow-wave sleep
TC	Thalamocortical
TRN	Thalamic reticular nucleus
TST	Total sleep time
UARS	Upper airway resistance syndrome
VLPO	Ventrolateral preoptic area

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Erklärung zur wissenschaftlichen Lauterkeit

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- Rudzik, F., Thiesse, L., Pieren, R., Wunderli, J.M., Brink, M., Foraster, M., Héritier, H., Eze, I.C., Garbazza, C., Vienneau, D., Probst-Hensch, N., Röösli, M., & Cajochen, C. (2018). Sleep spindle characteristics and arousability from night-time transportation noise exposure in healthy young and older individuals. *Sleep, 41*(7). doi: 10.1093/sleep/zsy077
- Rudzik, F., Thiesse, L., Pieren, R., Héritier, H., Eze, I.C., Foraster, M., Vienneau, D., Brink, M., Wunderli, J.M., Probst-Hensch, N., Röösli, M., Fulda, S., & Cajochen, C. (2019). Ultradian modulation of EEG arousals during sleep: effects of age and exposure to nighttime transportation noise. Submitted to *Sleep*.
- Rudzik, F. (2019). Age-dependent modulation of the arousal response hierarchy during sleep and its reactivity to nighttime transportation noise exposure.

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Franziska Helen Rudzik