



MASTERTHESIS

CONTRIBUTION OF SOUND IN THE INTENSIVE CARE UNIT ENVIRONMENT TO SLEEP DISRUPTION

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PREFACE AND ACKNOWLEDGEMENTS

In the period from March 2016 to March 2017 I worked on this master's assignment at the department of Intensive Care Medicine of the University Medical Center Groningen (UMCG). Working in the fields of sleep research and acoustics was challenging but also very interesting and I have learnt a lot the past year.

I would like to thank my supervisors Jaap Tulleken and Laurens Reinke for their inspiration and help during the whole project and Wim Dieperink (UMCG) for his support and help with organizing the practical side of the project. I would like to thank Han van der Hoeven (UMCG) for his advice on the polysomnography measurements and for manually scoring the recordings and Ciska Heida for her technical supervision. I also want to thank Nienke Idsardi for her help with the inclusions and measurements of healthy subjects during her 10 week internship at our department.

Secondly, I would like to thank the people from Philips Research Eindhoven for their input while setting up the study with healthy volunteers. They also made it possible for me to loan some equipment to perform and analyze the measurements.

Finally, I would like to thank Marleen Groenier for supervising my personal development and my family for their mental support. Thanks also to everyone who is not mentioned here but has in any way been involved with the project.

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ABSTRACT

Introduction: We know from the literature that patients admitted to an intensive care unit (ICU) are exposed to several intrinsic and extrinsic sleep disruptive factors, causing disturbed sleep. This may have detrimental effects on patient cognition and behaviour. Because so many factors play a role, studying the primary effects of the busy ICU environment is complicated. The current evidence on the effects of noise on the quality of sleep is subject to considerable risks of bias.

Methods: 37 ICU patients from our ICU at the University Medical Centre Groningen were included in a study into the relation between sleep and ICU sound. We also designed and conducted an experiment in which healthy volunteers slept in the ICU in order to study the relative contribution of the ICU environment on sleep. Thus far 3 subjects have completed both a home and ICU measurement night. Sleep was assessed using polysomnography.

Results: In ICU patients we found fragmented and disturbed sleeping patterns and high noise levels with frequent spikes. In the healthy subjects we found that 2 out of 3 showed reduced sleep quality under ICU conditions compared to at home. Measured sound levels at the bedside were lower than in our patient study and the number of sound events was also greatly reduced. Although light levels were comparable between the home and ICU setting the ambient temperature was much higher in the ICU. This may also have influenced sleep quality. For both patients and healthy subjects no correlation was found between sound events and arousals from sleep.

Conclusion: Noise levels in the ICU are high and sleeping patterns are disturbed. However, there are still a lot of uncertainties about the contribution of the ICU environment to sleep disruption. Because of the highly complex nature of acoustics and its mechanisms to influence sleep it is not possible at this moment to indicate which direction to take in reducing noise in the ICU. Inclusion of more healthy subjects into studies that measure sleep in an active ICU are necessary, as well as attention to correct reporting of acoustic parameters and settings and more extensive analysis of the sound environment.

LIST OF ABBREVIATIONS

EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ICU	Intensive Care Unit
$L_{A/C/Z}$	A/C/Z frequency weighting
$L_{F/S/I}$	Fast/Slow/Impulse time weighting
L_{eq}	Equivalent continuous noise level
L_{max}	Maximum sound level measured during the measurement period
L_n	Sound level that is exceeded n% of the time
L_{peak}	Maximum sound level reached at any instant during the measurement period
NREM	Non-Rapid Eye Movement
PSG	Polysomnography
R&K	Rechtschaffen & Kales
REM	Rapid Eye Movement
SPL	Sound pressure level
SWS	Slow Wave Sleep
TST	Total Sleep Time
WHO	World Health Organisation

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CHAPTER ONE

GENERAL INTRODUCTION AND OVERVIEW

Out of 2 million patients being admitted for at least one night in the Netherlands in 2015, 85.000 were admitted to an intensive care unit (ICU) ^{1,2}. The median length of treatment in the ICU is 1.1 days, with 25% of patients staying 2.9 days or longer ¹.

During their stay in the hospital many patients experience sleeping difficulties. Their sleep is often fragmented and the quality of sleep is reduced compared to their sleep at home. At the same time patients have an increased need for sleep because their body is dealing with disease or injury ³.

1.1 Aim of this study

The aim of this master's project was to expand the knowledge about the relation between noise in the ICU environment and sleep disruption. The study was divided into four parts, each with a different purpose. In part 1 we evaluated what is already known by performing a structured review of the literature. In part 2 we discuss the clinical and technological background of sleep and sound measurements. In part 3 the characteristics of sound in the ICU and the correlation to sleep in patients was examined. In part 4 the preliminary results from a study comparing the quantity and quality of sleep in healthy subjects in the ICU and home environment is presented.

1.2 Structure of this thesis

This thesis consists of 3 research chapters supplemented with a theoretical frame and general discussion and conclusions.

- Chapter one: general introduction to the topic of research, aim of this study and structure of the thesis.
- Chapter two: systematic review of the literature.
- Chapter three: clinical background about sleep neurobiology and environmental impact factors and technical theoretical basis of sleep measurements and sound measurement.
- Chapter four: the results from sound analysis in the ICU and the correlation with patients' sleep.
- Chapter five: the results from sleep recordings of healthy subjects in the ICU and home environment.
- Chapter six: in this final chapter the overall results are discussed, conclusions are drawn and recommendations are made.

CHAPTER TWO

SYSTEMATIC REVIEW SLEEP AND NOISE IN THE ICU

2.1 Introduction

Sleep is an important process that is essential for repair and survival ⁴. Disrupted sleep is associated with impaired immune function and increased susceptibility to infections ⁵⁻⁷ alterations in nitrogen balance and wound healing ^{5,7} and diminished neurophysiologic organization and consolidation of the memory ⁶. In the intensive care unit (ICU) this may lead to delirium, prolonged admission and mortality ⁶. However, most patients in the ICU have disturbed sleeping patterns ^{4,5} characterized by severe fragmentation of sleep ⁸.

Patients admitted to an ICU are exposed to several intrinsic and extrinsic sleep disrupting factors. Intrinsic factors are mostly related to the critical illness itself, but may also include pre-existing sleep pathologies or disturbed circadian rhythm. Extrinsic factors disturbing sleep are mostly environmental in nature, such as uncomfortable temperatures, high levels of noise and light, and frequent medical and nursing interventions throughout the day and night. A multitude of these factors, most of them interdependent, likely cause disrupted sleep in the ICU. The incidence of sound peaks may depend on the frequency of ICU-staff activities, which in turn depends on disease severity of the individual patient. However, the precise contribution of each factor remains unclear ^{6,9,10}. The environmental stimulus that is often associated with disturbed sleep is noise ^{11,12}, although its impact on sleep is still debated.

The 1999 World Health Organization (WHO) guidelines for community noise recommend a maximum of 40 dB(A) (decibels, adjusted for the range of normal hearing) overnight for hospital environments. However, from a study performed by Darbyshire et al. ¹³ it became clear that this is not achievable in a modern ICU since they were only able to achieve such low levels in a side room by switching all equipment off. Consequently, sound levels in ICUs far exceed World Health Organisation (WHO) recommended levels ¹³⁻¹⁸. Average noise levels between 55 dB(A) and 70 dB(A) are common, as are peak noise levels of more than 80 dB(A) ¹⁹.

2.1.1 Objectives

An increasing number of studies focus on sleep disturbance by ICU noise specifically. Sample sizes are often small and many confounding factors potentially skew results. To control confounding, a substantial portion of studies have been investigating healthy volunteers in simulated ICU environments. To our knowledge, no systematic review of the impact of ICU noise on the quality of sleep of healthy volunteers or ICU patients has been published. We therefore, systematically reviewed relevant studies of the effects of ICU noise on the quality of sleep in healthy volunteers and ICU patients. The primary goal was to determine the significance of ICU noise in the ever growing field of ICU sleep research and to review the level of evidence supporting the findings.

The following questions were used to guide the selection of relevant articles:

- How is the quality of sleep in healthy volunteers affected by the ICU sound environment?
- Is there a relationship between quality of sleep and the ICU sound environment in ICU patients?
- What are the priorities for future research?

2.2 Methods

The Cochrane Collaboration method for non-randomized studies was used for this review²⁰.

2.2.1 Eligibility criteria

We searched for studies assessing sleep of adult patients and healthy volunteers in the ICU environment using an objective method, such as polysomnography (PSG) or Actigraphy, or patient self-reports while the patient was in the ICU, whilst recording sound levels. Studies were excluded if they met at least one of the following criteria: included only neonates or children, assessed sleep using observation only or did not objectively measure sound levels. Measuring sleep by observation is an unreliable method that is known to significantly overestimate total sleep time and sleep continuity and is generally considered to be incapable of accurate estimation of the quality of sleep²¹. Finally, it is vital that sound levels are objectively measured using standard units to ensure that results from various studies can be compared. The primary outcome was the change in the number of arousals for different sound conditions. This outcome was chosen because it best represents sleep quality in a single measure.

2.2.2 Search strategy

A literature search was conducted using the following electronic databases: Scopus, Pubmed, EMBASE, CINAHL, Web of Science and the Cochrane Library. The search terms used in all of the databases were 'sleep AND (noise OR sound) AND (ICU OR intensive care OR critical care)'. The search was conducted without any article format, data or language restrictions and included studies published until august 2016.

2.2.3 Study selection

The titles for the articles retrieved from the search were manually reviewed by two authors. After removal of letters to the editor, reviews, abstracts only and non-article formats, remaining abstracts were assessed for eligibility. Only abstracts of original investigations were included. The references of all included articles as well as those from selected reviews were checked for relevancy. The following data were extracted: year of publication, country in which the study was conducted, period of conduct of the study, inclusion and exclusion criteria, all outcomes, details on interventions and characteristics of the studies.

2.2.4 Bias risk assessment

Two authors independently assessed the risks of bias of the studies following the domains from the Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions²². The domains are: bias due to confounding, bias in selection of participants into the study, bias in measurement of interventions, bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported results.

2.2.5 Statistical analysis

We performed the meta-analyses using the software package Review Manager 5.3²³. Results were presented as mean difference with 95% confidence interval (CI). We calculated a random-effects model. Heterogeneity was explored by the Chi-squared test with significance set at a P value of 0.05. The quantity was measured with I^2 .

2.3 Results

The search returned 1373 hits. After removal of duplicates 830 citations remained. After screening of titles and abstracts, a total number of 37 full-text articles were retrieved. Of these, a total of 18 papers from 16 studies met the eligibility criteria. A manual search of the references of the included articles and of 34 relevant reviews resulted in the inclusion of 4 more relevant reviews whose reference lists were also searched. A flow chart of study inclusion is presented in Figure 1.

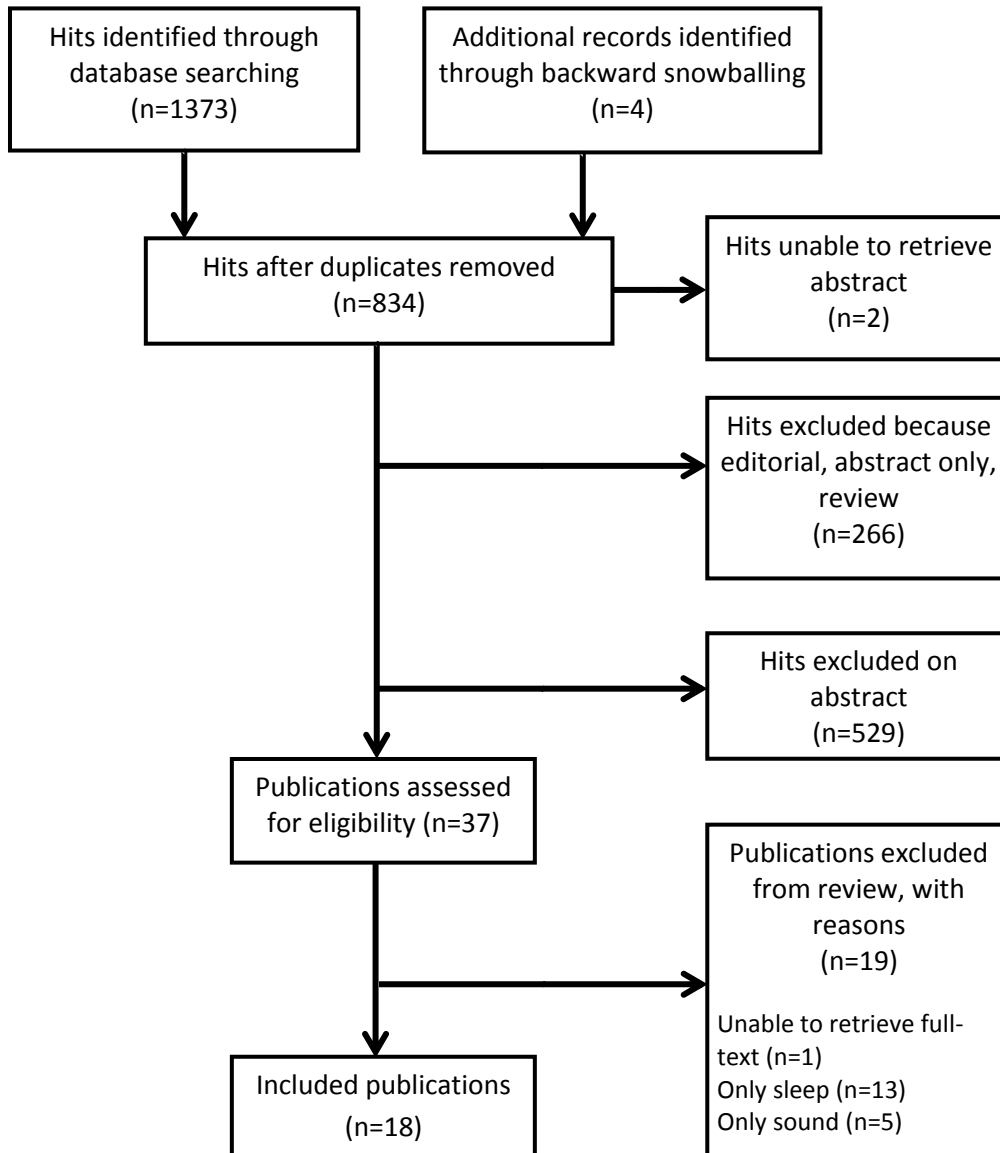


Figure 1: Flow chart of study inclusion

2.3.1 Study characteristics

Patients

9 papers on outcomes from 8 studies concerning patients were retrieved with a total number of 569 included patients. However, outcomes were only reported on data from 267 subjects. 302 subjects did not complete the study they were in, of which 279 dropped out of the study by Patel et al.²⁴. 4 studies were observational^{11,25-27}, 2 were cross-over studies^{28,29}, 2 studies used a before- and after

intervention design ^{24,30} and 1 was a randomized controlled trial ³¹. Further characteristics on the studies can be found in Table 1.

Healthy volunteers

10 papers on outcomes from 9 studies concerning healthy volunteers were found with data on 263 subjects from a total of 268 included. 5 had repeated measures designs ^{29,32-35}, 2 were cross-over studies ^{25,36} and 2 used a posttest only control group design ^{37,38}. Further characteristics on the studies can be found in Table 2.

2.3.2 Bias risk assessment

Patients

0 studies had low risk of bias for confounding (0%), 4 studies had low risk of selection bias (50%), 0 studies had low risk of measurement bias (0%), 4 studies had low risk of bias due to departures from intended interventions (50%), 6 studies had low risk of bias caused by missing data (75%), 3 had a low risk of outcome bias (38%) and all studies had low risk of reporting bias (100%). These results are summarized in Figure 2a.

Healthy subjects

4 studies had low risk of bias for confounding (44%), 7 studies had low risk of selection bias (78%), 0 studies had low risk of measurement bias (0%), 8 studies had low risk of bias due to departures from intended interventions (89%), 4 studies had low risk of bias caused by missing data (44%), 4 had a low risk of outcome bias (44%) and 6 studies had low risk of reporting bias (67%). These results are summarized in Figure 2b.

Table 1: Characteristics of included studies: patients

Author (year published)	Design	Method	No patients (included)	Mean age \pm sd	Mean duration of ICU stay before study \pm sd	Noise level	Studied intervention	Quality of sleep related to sound environment?
Bosma (2007)	Cross-over	Night PSG	13 (16)	63 \pm 13	22 \pm 11	<u>Night</u> Mean _{10 min} \approx 60 dB Max _{10 min} \approx 90 dB	Ventilator modes	Patient ventilator discordance causes sleep disruption.
Elliott (2013 and 2014)	Observational	24 h PSG RCSQ	53 (57)	60 \pm 20	5 (IQR 2.5-11)	<u>Day</u> <u>Night</u> Leq,1 sec 54 dB(A) Leq,1 sec 50 dB(A)	-	Results suggest that a sound reduction program is required.
Freedman (2001)	Observational	24 h PSG	22 (24)	61 \pm 16	18 \pm 20	<u>Day</u> Mean _{1 min} 59 dB(A) Max _{1 min} 69 dB Peak _{1 min} 86 dB <u>Night</u> Mean _{1 min} 57 dB(A) Max _{1 min} 65 dB Peak _{1 min} 83 dB	-	Impact of environmental noise appears much less important than previously described.
Gabor (2003)	Observational	24 h PSG	7	57 \pm 19	48 \pm 40	<u>Day</u> Mean 56 dB Max 66 dB <u>Night</u> Mean 54 dB Max 61 dB	-	Only 30% of observed sleep disruption was accounted for by sound and patient-care activities.
Hu (2015)	RCT	RCSQ	45 (50)	57 \pm 11	2 \pm 1	<u>Night</u> Mean 70 dB(A)	Earplugs and eye masks and relaxing background music	Studied intervention is useful for promoting sleep.
Li (2011)	Before- and after intervention	RCSQ	55 (60)	50 \pm 3	-	<u>Night</u> <u>Before</u> Mean 58 dB Peak 59 dB <u>After</u> Mean 50 dB Peak 51 dB	Change night-time nursing routines, decrease noise level and dim lights during night	Environmental noise and night-time medical and nursing care activities clearly play a role in disrupting sleep.
Patel (2014)	Before- and after intervention	RCSQ	59 (338)	61 \pm 15	7 \pm 3	<u>Night</u> <u>Before</u> Mean 69 dB <u>After</u> Mean 62 dB	Multicomponent bundle of interventions to reduce noise and light exposure and care activities at night	Significant improvement in patients' perception of sleep.
Wallace (1998)	Cross-over	Night PSG	13 (17)	57 \pm 20	13 \pm 8	<u>Night</u> Mean SPL 58 dB(A)	Earplugs	All subjects experienced severely disturbed sleep, with or without earplugs.

Table 2: Characteristics of included studies: healthy volunteers

Author (year published)	Design	Method	Number of patients completed study (included)	Age	Average noise levels	Studied intervention	Quality of sleep related to sound environment?
Gabor (2003)	Cross-over	24 h PSG Questionnaire	6	Range 23-65	<i>Single-patient room</i> <u>Day</u> Mean 44 dB Max 55 dB <u>Night</u> Mean 43 dB Max 49 <i>Open-plan ICU</i> <u>Day</u> Mean 56 dB Max 67 dB <u>Night</u> Mean 56 dB Max 61 dB	Single-patient room vs open-plan ICU bed	Subjects slept relatively well. Noise accounted for a significant proportion of sleep disruption, but not to pathologic extent.
Hu (2010)	Repeated measures	Night PSG VAS	14 (15)	31 ± 16	<u>Night</u> <i>Baseline</i> Mean 34 dB(A) <i>Noise</i> Mean 66 dB(A)	Quiet vs recorded ICU noise vs recorded ICU noise with earplugs and eye masks	With noise and light conditions subjects had poorer perceived sleep quality and suffered from sleep disruption.
Huang (2015)	Cross-over	Night PSG VAS	40 (40)	41 ± 12	<u>Night</u> <i>Baseline</i> Mean ? <i>Noise</i> Mean 67 dB(A)	Quiet vs recorded ICU noise and light conditions	Nocturnal sleep is disturbed in healthy subjects with exposure to simulated ICU noise and light.
Persson (2013)	Repeated measures	Night PSG Questionnaire	17 (18)	23 (18-30)	<u>Night</u> <i>Baseline</i> L _{Aeq} 20.0 dB(A) L _{A50max} 21 dB (A) <i>ICU</i> L _{Aeq-7} 45.47 dB(A) L _{A50max} 64 dB(A) (exposure)	Quiet vs recorded ICU noise – 7 dB vs recorded ICU noise peak reduced	The ICU sound condition significantly impaired the restorative functions of sleep. Subjective data supported PSG findings.

Table 2: Continued

Author (year published)	Design	Method	Number of patients completed study (included)	Age	Average noise levels	Studied intervention	Quality of sleep related to sound environment?
Snyder (1985)	Repeated measures	Questionnaire	10	Range 20-24	<u>Night</u> Baseline Mean < 65 dB Noise Mean 76 dB	Quiet vs recorded ICU noise	Physical and physiological alternations can occur when noise interferes with sleep.
Stanchina (2005)	Repeated measures	Night PSG Subjective sleep quality	5 (8)	27 ± 2	<u>Night</u> Baseline Mean ? Noise Mean 58 dB Noise+white noise Mean 61 dB	Quiet vs recorded ICU noise vs recorded ICU noise with white noise	Peak noise was not the main determinant of sleep disruption. Percent of arousals associated with noise substantially greater compared to recent reports.
Topf (1992 and 1993)	Posttest only control group	Questionnaire	105	36	<u>Night</u> Baseline Mean ? Noise Mean 56 dB Max 87 dB	Quiet vs recorded ICU noise vs recorded ICU noise with personal control over noise	Convincing support for causal relationship.
Topf (1996)	Posttest only control group	Questionnaire	60	36	<u>Night</u> Baseline Mean ? Noise Mean 56 dB Max 87 dB	Quiet vs recorded ICU noise	Support for the hypothesis that subjects exposed to ICU sounds exhibit poorer sleep.
Wallace (1999)	Repeated measures	Night PSG	6	25 ± 3	<u>Night</u> Baseline Mean 38 dB(A) Noise Mean 62 dB(A)	Quiet vs noise vs quiet with earplugs vs noise with earplugs	Results suggest that sleep is disrupted by exposure to simulated ICU noise and use of earplugs results in more REM sleep.

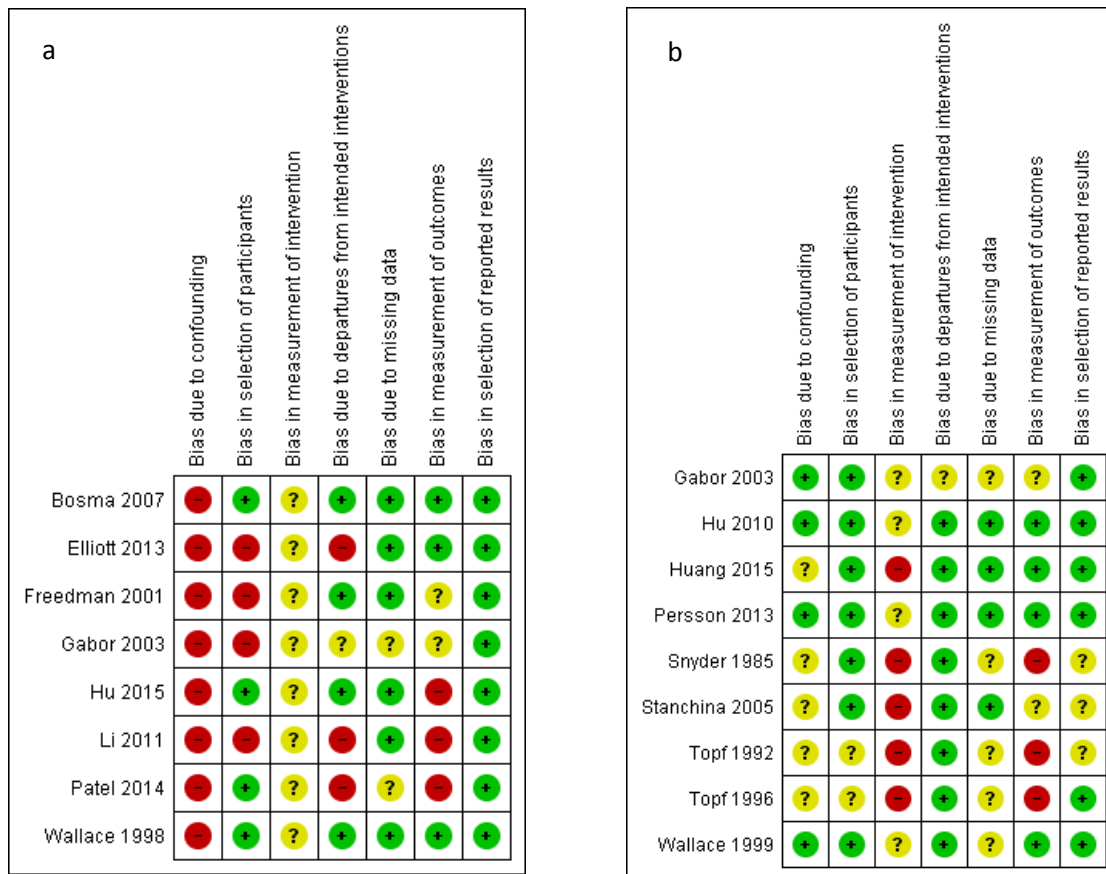


Figure 2: Risk of bias assessment patients studies (a) and healthy volunteers (b). Green is low risk, red is high risk, yellow is unknown.

2.3.3 Outcomes

The mean differences with the 95% CI of the outcome number of arousals are presented in Figure 3 for all studies comparing a baseline setting with an ICU noise setting. This was only the case for studies with healthy volunteers. 6 studies with 86 subjects reported the number of arousals. For the study by Gabor et al.²⁵ the baseline condition was a single room and the ICU noise condition an open ICU. For all other studies the baseline condition was a quiet environment in a sleep laboratory and the ICU noise condition consisted of ICU noises played back in the same sleep laboratory. Persson et al.³³ reported the total number of arousals for the study night, while in the other studies the arousal index (number of arousals per hour) was reported. There was a significant difference in number of arousals between baseline and the ICU noise condition (mean difference 9.59; 95% CI 2.48-16.70). There was however also considerable heterogeneity (I^2 94%, $P < 0.00001$).

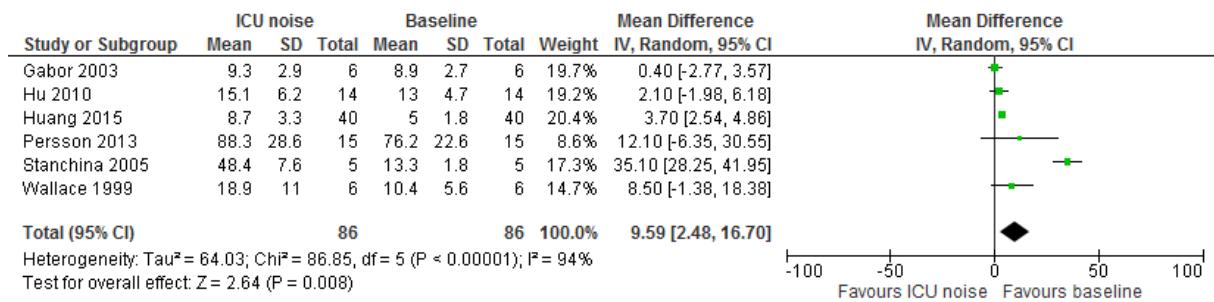


Figure 3: Forest plot of comparison of arousal (index) during baseline and ICU noise condition. Size of squares for mean difference reflects the weight of the study in the pooled analyses. Horizontal bars span the 95% confidence intervals.

2.4 Discussion

Our review on the effect of noise on sleep in the ICU found that ICU noise has a significant effect on the occurrence of arousals in healthy volunteers. The considerable heterogeneity may be caused by the large differences in study protocols. 18 studies fulfilled our inclusion criteria, of which 8 contained data on patients and 9 on healthy volunteers. It was not possible to perform a meta-analysis on the data from patient studies because there were no studies that reported objective sleep measurements from multiple groups under different sound conditions.

The current evidence of the effects of noise on the quality of sleep is subject to considerable risks of bias. Because sleep disruption in ICU patients is multifactorial, it is hard to correct for confounders. In healthy subjects this is less of a problem because they are not affected by an underlying illness. It can often be difficult to include patients for this kind of studies, because many patients and their family do not want the added burdening and refuse to participate. This can cause selection bias, especially if a small number of patients was included over a relatively long period. However, because most studies reviewed used a repeated-measures or crossover design, many were assessed as having low risk of selection bias. Sound levels were not always measured for all groups, leading to high risk of measurement bias. Furthermore, the outcomes of sound measurements are known to often be computed incorrectly¹⁶, but we were not able to determine the exact method of sound data analysis in most papers. Some studies required nurses to keep a record of each patient care activity while a few others placed dedicated observers in the ICU. This poses the risk that environmental conditions were altered in a way that was not intended. The study of MacKenzie et al. focused on the sources of noise in the ICU mentions that the hospital staff suggested that the noise levels during the period when observers were present were not as high as normally experienced¹⁵. This effect that external observers have on the behavior of those observed is known as the Hawthorne effect. The Hawthorne effect is especially important in studies assessing the effectiveness of an implemented intervention, such as noise reduction. If personnel, even unconsciously, already altered their behavior because they have been made aware of the topic of noise and interruptions, effects cannot be measured reliably and representatively. Furthermore, not all papers mentioned if or which data were missing. Risk of bias in the measurement of outcomes was considered high when subjective methods, such as questionnaires, were used. The intuitive relation between noise and sleep disruption is common knowledge, thus subjects can be expected to have preconceptions, further increasing the risk of bias when instructed on the goals of the study. Another thing we looked at is whether the PSG recordings were scored blind or not. This is important in studies with multiple groups but it was not applied in all

studies with such a design. Finally, very few indications of bias in selection of reported results were found.

Because of these concerns it is difficult to determine the true effect of noise in the ICU environment on sleep in patients. Although a significant effect was found in healthy volunteers all but one of these studies were performed in a sleep laboratory and not in the actual ICU. In recordings of healthy volunteer's sleep around 60%²⁵ of arousals were immediately preceded by noise events, while several studies in ICU patients have reported that only 11% to 30% of sleep disruptions observed in the electroencephalogram (EEG) could be attributed to environmental noise^{11,39}. This suggests that other factors present in patients might be more profound in disturbing sleep.

The importance of other ICU related factors on the observed disturbance of sleep is also suggested by the results from a recently published Cochrane Review by Hu et al.⁴⁰ on the efficacy of non-pharmacological interventions for sleep promoting in critically ill adults. They found some evidence that these interventions can provide small improvements in subjective measures of sleep quality and quantity, but the quality of the evidence was low. The effects on objective sleep outcomes were inconsistent across 16 studies. 4 of the studies investigated the use of earplugs or eye masks or both in a total of 141 subjects. In the majority of these studies no benefit was found. The cause of non-response to these interventions remains unclear, although the high risk of bias probably contributed.

For future investigation of the relation between sound and sleep, we recommend sufficiently large sample sizes. Half of the studies included in this review had a sample size of no more than 20 subjects, which precludes detailed analysis. Because there are so many difficulties to measure confounders present in the ICU patient population, studies focusing on healthy volunteers in the real ICU environment, or a combination of healthy volunteers and patients in the same study, are best suited to study to what extent noise is a sleep disruptive factor in the ICU. It is also important to give special attention to complete and correct execution and description of sound measurements to facilitate pooling of data and meta-analysis. Measurement procedures are often unclear with limited specification of parameters, used time constants, frequency weighting used and averaging type. Further, most studies only focus on noise amplitude. Very little research has been performed in ICU settings on the relationships between sleep quality and other acoustic parameters, such as the acoustic spectrum, reverberation time, perceived loudness and entropy. Sound spectrum, which shows the relationship between sound level and frequency, is important for sound perception. Reverberation time is defined as the time needed for the sound to decay 60 dB after the source has stopped⁴¹. Reducing the reverberation time 'smoothes' sound stimuli, which may play an important role in reducing the impact of environmental noise on sleep, as is shown by Berg et al.⁴². Finally, the information density of sound is also critical for the amount of disturbance^{11,43}. Sounds that have a specific meaning, like spoken language, are more likely to evoke a EEG potential. Finally, it is important for future studies to focus on using objective measurement methods and ensure that PSG scoring is performed blinded as much as possible. Although PSG is an objective measuring method the scoring of sleep stages is still a manual process whereby bias can be introduced if datasets are not presented randomly.

2.5 Conclusion

The current evidence on the effects of noise on the quality of sleep is subject to considerable risks of bias. Because sleep disruption in ICU patients is multifactorial, it is hard to correct for confounders. Half of the studies had a sample size of no more than 20 subjects. Sound levels were not always measured for all groups. Furthermore, the presented parameters of sound measurements vary among studies and certain details are often lacking. Thereby it is questionable whether all were computed correctly. Future studies need to include sufficiently large sample sizes and give special attention to complete and correct execution of sound measurements to facilitate pooling of data and meta-analysis. Because of the highly complex nature of acoustics and its mechanisms to influence sleep it is not possible at this moment to indicate which direction to take in reducing noise in the ICU.

CHAPTER THREE

CLINICAL AND TECHNOLOGICAL BACKGROUND

Now that we know which issues arise from the literature, let's look into the clinical and technological background of sleep and sound measurement.

3.1 Sleep neurobiology

Sleep can be divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep^{6,9}. Based on the criteria first formulated by Rechtschaffen and Kales (R&K)⁴⁴ NREM sleep can be divided further into three stages, N1, N2 and N3, based on the presence of features such as specific frequency bands, sleep-spindles and K-complexes in the electroencephalogram (EEG). The stage N3, also known as slow-wave sleep (SWS), and REM are believed to be most important for the restorative function of sleep⁶. During sleep the different sleep stages occur sequentially in cycles of around 90 minutes each in healthy subjects^{6,9}. The overall 'sleep quality' is difficult to express because there is no established definition for it⁴⁵. However, besides depth of sleep, sleep quality seems to be a matter of sleep continuity⁴⁶.

However, most ICU patients have disturbed sleeping patterns, as is shown in numerous studies using polysomnography (the gold standard for evaluating sleep)^{4,5,47,48}. These sleep disturbances are characterized by severe fragmentation and frequent arousals and awakenings^{8,47}. An arousal is defined as a wake period of between 3-10 seconds, after which sleep resumes. One study described a median duration of sleep without waking of only 3 minutes²⁷. The sleep architecture is disturbed with more stage N1 and N2 sleep present, while the critically important SWS and REM sleep stages are less prevalent^{7,9,27}. Further, it has been reported that ICU patients spend up to half of their total sleep time during the daytime^{7,27,47,49}. Finally, the traditional R&K sleep scoring criteria are often not uniformly applicable in critically ill patients because of the presence of atypical EEG activity^{8,50}.

Disrupted sleep in humans is associated with impaired immune function, increased susceptibility to infections⁵⁻⁷ alterations in nitrogen balance, impaired wound healing^{5,7} and impairment of neurophysiologic organization and consolidation of memory⁶. In ICU patients this may consequently lead to the development of delirium, prolonged admission and increased mortality risk⁶. Clearly, sleep is essential for human homeostasis, recovery and survival⁴.

3.2 The ICU environment and sleep

Patients admitted to an ICU are exposed to several intrinsic and extrinsic sleep disruptive factors. Intrinsic factors are mostly related to the critical illness itself, such as pain, medication and care interventions, and resulting conditions like a disturbed circadian rhythm. This disturbance of circadian rhythm is thought to be important in the observed changes in distribution of sleep over the day. Extrinsic factors are environmental, such as uncomfortable temperature and high levels of noise and light during the night, and medical interventions. A multitude of these factors, most of them interrelated, is thought to play a role in the observed disruption of sleep in the ICU. However, the precise contribution of each factor remains unclear^{6,9,10}.

In all ICUs sound levels are much higher than recommended by the WHO for hospitals, as is shown in many studies¹³⁻¹⁸. Hospital noise levels have increased consistently since the 1960's. The average daytime and nighttime L_{Aeq} in hospitals have risen from 57 dB(A) (decibels, adjusted for the range of

normal hearing) and 42 dB(A) in 1960 to 72 dB(A) and 60 dB(A) in 2005. This is 20-40 dB(A) higher than the guidelines of the WHO recommend. Because in an ICU patients are monitored and cared for around-the-clock it is noisy 24 hours a day ¹⁶. However, the relative contribution of this environmental factor to sleep disturbance in ICU patients is difficult to assess. In patients, researchers have only been able to correlate 10-40% of arousals and awakenings to sudden peaks in sound ^{11,25}. Additionally, patients in critical care settings have limited or no exposure to circadian rhythm stimuli such as bright light ⁵¹. Artificial lighting is of insufficient intensity and the timing of light exposure is often counterproductive because exposure at night, even at lower intensities, has an adverse effect on sleep timing ⁵¹. Further, studies examining the effectiveness of sleep promoting interventions show various results ranging between deterioration and relative improvements of 10% to 68% ⁴¹, using various approaches such as behavioural modification, earplugs, eye masks, sound masking by adding other sounds, and improving absorption using acoustic materials. In one study, sleep quantity and quality even seemed to be less after implementation of behaviour modifications ⁵². The causes of non-response to these interventions observed in some patients remains unclear ^{52,53}.

3.3 Effects of sleep deprivation

Loss of sleep is known to have an effect on numerous parts of the body. The most well-known symptoms are lack of energy and enthusiasm, daytime sleepiness, increased irritability, confusion and decreased short-term memory ⁵⁴. Changes in mood are the most prominent manifestation. Negative reactions to unpleasant experiences are magnified, while positive experiences are easily forgotten ⁵⁴. Sleep deprivation also reduces the ability to make competent decisions and can cause added anxiety and even pain. Although the effects of sleep loss on the immune system remain largely unclear there are indications that sleep deprivation alters the immune response and can increase circulating levels of inflammatory markers. An increase in sympathetic and decreased parasympathetic modulation leads to increased blood pressure and risk to acute myocardial infarction. Sleep deprivation intensifies the stress response and leads to an elevated metabolic rate. ^{4,54}

3.4 Polysomnography

Sleep is an active brain process. Therefore the investigative approach for studying sleep involves measuring brain activity. The first overnight electroencephalogram (EEG) sleep recordings were done in the 1930's. To reduce the amount of data the tracings were summarized using sleep stages based on the presence of particular EEG activity. EEG activity can be divided into beta activity (>13 Hz), sleep spindles (bursts of 12-14 Hz), alpha rhythm (8-13 Hz), theta rhythm (4-7 Hz), delta rhythm (<4 Hz) and slow waves (<2Hz). At first, every laboratory used their own scoring system. This changed when the first standardized manual was published in 1968. Since then, only minor changes have been implemented regarding the sleep stages already mentioned in the previous chapter: Wake, N1, N2, N3 and REM sleep. EEG activity is recorded using 4-5 channels, as well as electrooculography (EOG) activity from the right and left eye and electromyography (EMG) activity from the jaw muscles. The electrodes are attached to the scalp of the subject according to the international 10-20 standard system. For most PSG recordings these are: F3, A1, A2, C3, C4, O1, ground (G) and reference (CZ) as depicted in Figure 4. A1 and A2 are placed just above the left and right ear. ⁵⁵

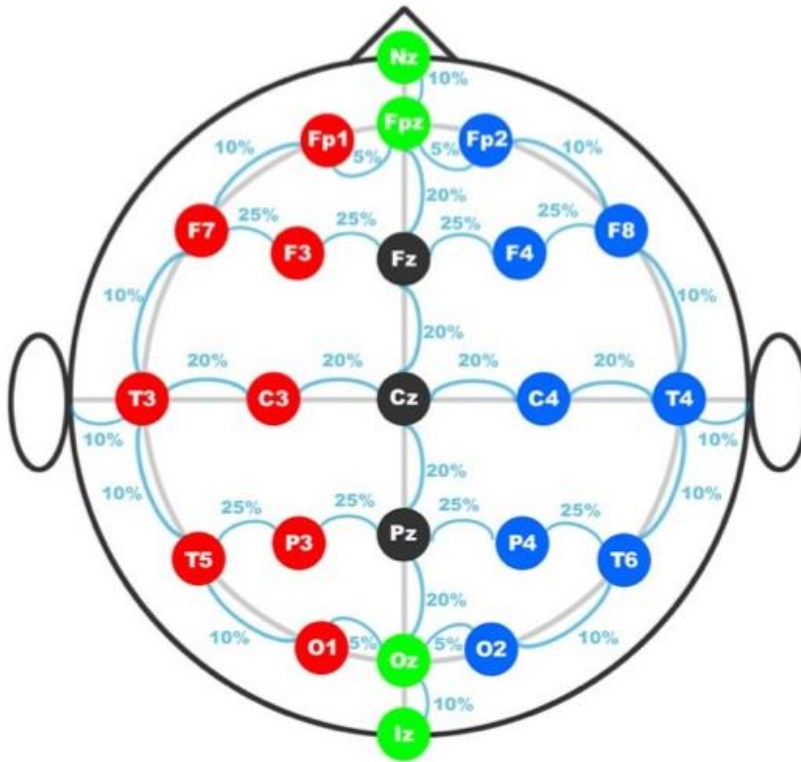


Figure 4: Scalp electrode sites used for polysomnography⁵⁶

Sleep stages are scored per epoch of 30 seconds of recording. During wakefulness with eyes closed the predominant rhythm is alpha activity. N1 is the first stage of sleep and is scored when no more than 50% of the epoch contains alpha activity and no characteristics of other sleep stages are present. The predominant pattern is theta activity. Stage N2 is scored when there are sleep spindles or K-complexes, but delta activity totals less than 20% of the epoch. Examples of characteristic EEG features for sleep stages are shown in Figure 5. Stage N3 is scored when an epoch contains more than 20% delta or slow wave activity. Finally, REM sleep is scored when rapid-eye movements are present in the EOG, the EMG activity is very small and the EEG pattern shows stage N1 characteristics. Further also arousals can be scored. An arousal is an abrupt change from sleep to wakefulness, or from a 'deeper' sleep stage to a 'lighter' stage, lasting between 3 and 15 seconds. If the arousal has a duration of more than 15 seconds it is called an awakening (and stage wake is consequently scored because more than 50% of the epoch contains wake EEG).⁵⁵

Electroencephalogram (EEG) showing typical brain waves of sleep and wakefulness

wakefulness (relaxed state)

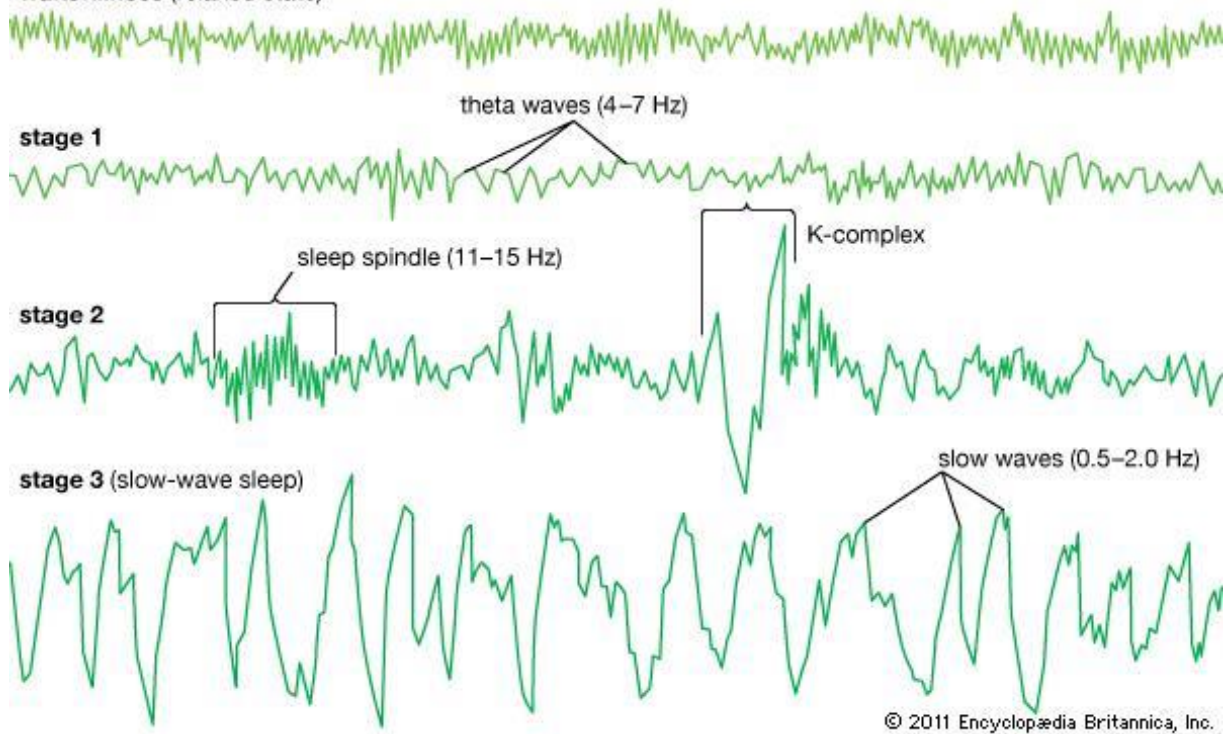


Figure 5: Characteristic EEG features for sleep stages ⁵⁷

3.4.1 Polysomnography in ICU patients

Measuring and classifying sleep in the ICU is more complicated. In about one third of these patients the conventional scoring rules are difficult to use because of altered sleep and wake EEG patterns ⁴⁹. Conditions often seen in the ICU patients, such as renal failure, hepatic dysfunction and use of sedatives and analgesics, can be associated with significant EEG changes. So can the use of sedatives induce beta activity, which may lead to an overestimation of wake or N1 sleep. On the other hand, the often seen phenomenon of EEG slowing in critically ill patients may cause intrusion of delta waves into the wake state, leading to overestimation of sleep time ⁵⁸. Furthermore, the K-complexes and sleep spindles used to identify stage N2 are often absent ⁸.

Additionally, traditional assessments of sleep forego the highly fragmented nature of sleep in this patient population. Conventional sleep metrics focus on the total amount of sleep per stage for one night's sleep. These metrics include: total sleep time (TST), NREM and REM sleep duration or percentage, and number of awakenings and arousals per hour ⁴⁹. However, it has been proposed that a minimum period of 10 minutes uninterrupted sleep is needed to serve a recuperative function ⁵⁹. A minimal amount of light sleep continuity is thought to be needed before sleep deepens to N3 and cycles to REM sleep ⁴⁹. Drouot et al. have shown that percentage of time spent in sleep periods lasting less than 10 minutes might be a relevant indicator of the degree of sleep fragmentation among ICU patients ⁴⁹.

3.4.2 Automatic sleep classification using the Somnolyzer algorithm

Manual scoring is a time-consuming process and even with a lot of training high inter- and intra-scorer reliability is difficult to achieve with scoring of arousals and specific sleep stages such as N1⁶⁰. The Somnolyzer 24x7 system has been developed and validated using a large database of 94 healthy controls and 49 sleep disturbed patients by Anderer et al.⁶¹. The system uses a raw data quality check and feature extraction algorithms to identify density and intensity of patterns such as sleep spindles, delta waves and slow and rapid eye movements. It adheres to the decision rules for visual scoring as closely as possible and therefore a smoothing procedure for the start and end of stages REM and N2 was implemented. The epoch-by-epoch agreement between Somnolyzer and the human expert was found to be 80%, while the inter-rater reliability was 77%. A high validity was shown also on the target variable level. In a study by Punjabi et al.⁶⁰ it was found that the percentages for N1, N2 and N3 sleep found with Somnolyzer were consistently higher than any manually scored values, while the arousal index was mostly similar. However, because manual scoring can at best be considered an imperfect reference it is not possible to attribute differences between manual and automated scoring to one or the other because the source of the error (computer or human) is not known. These studies show the applicability of automated classification to assist in sleep scoring application in both research and the clinic^{60,61}.

3.5 Environmental sound measurement

Sound waves are essentially variations in pressure over time. The typical pressure threshold of perception of an average human is 20 μPa (pascal) at 1000 Hz in air. A painfully loud sound may be about 20 Pa at the same frequency, demonstrating the large dynamic range of human sound reception. Because there are thus about 12 orders of magnitude between the softest sound the human ear can detect and very loud sounds, sound pressure levels (SPL) are usually expressed on the logarithmic decibel (dB) scale. Further, our ears also respond logarithmically to changes in intensity. An increase of 10 dB is perceived as twice as loud, while an increase of 3 dB is just perceptible. The threshold of hearing is set at 0 dB. Other sound levels in decibels are expressed relative to this threshold using the following equation:

$$SPL = 20 \log_{10} \left(\frac{p}{p_{ref}} \right) dB \quad (1)$$

The normal range of human hearing is between 20 Hz and 20 kHz. Sound meters are capable of a flat frequency response over the entire range of human hearing, also known as Z-weighting. However, human hearing capabilities are not equal for all frequencies. Humans hear best at about 3500 Hz. A-weighting is the most common weighting and represents the response of the human ear, reducing the power of the lower and higher frequencies. There is also a C-weighting, resembling the flatter response of the human ear at sound levels above 100 dB. This weighting is therefore often used for peak measurements.^{62,63} The response of the different weightings is shown in Figure 6.

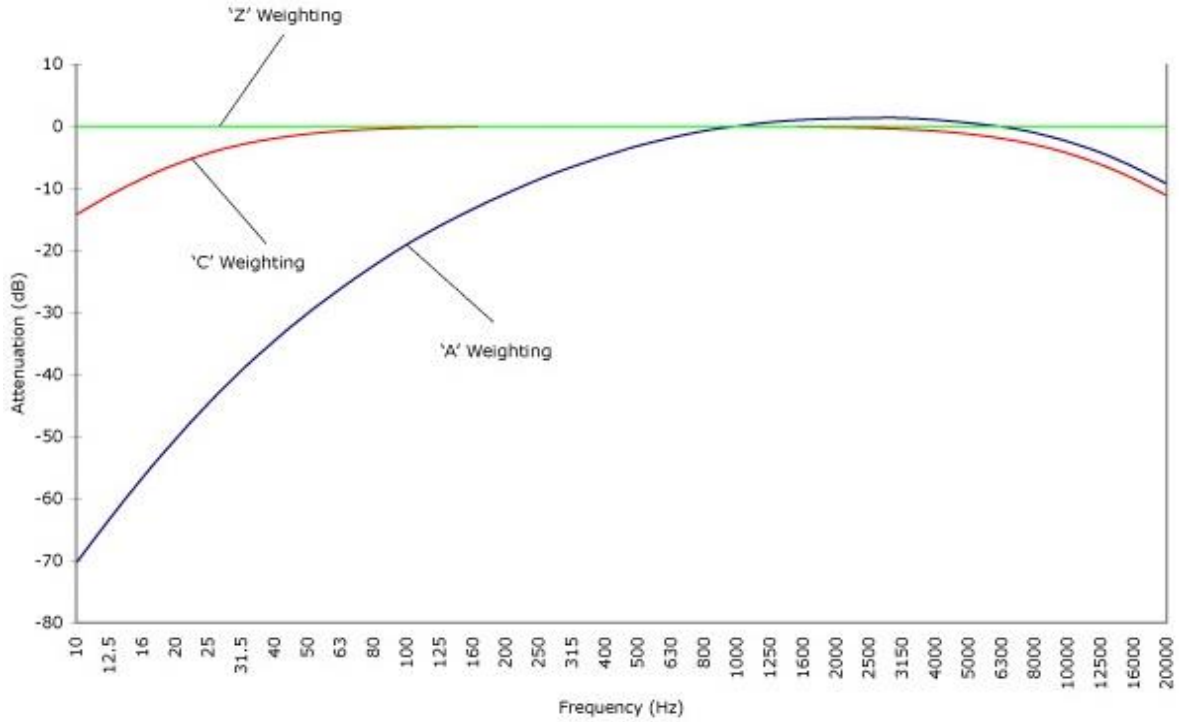


Figure 6: Response of Z, A and C weighting ⁶⁴

A wide range of parameters are available to assess environmental noise. Besides frequency weighting, there are also 3 time weightings available specifying the response times as fast (125 ms up and down), slow (1000 ms up and down) or impulse (35 ms up and 1500 ms down). The impulse response is not as common and is used in situations with sharp impulsive noises, such as explosions. The fast rise and slow fall time were implemented to mimic the perception of the human ear to these noises. $L_{Aeq,T}$ is the A-weighted equivalent continuous noise level measured over a time period T, as expressed in equation 2.

$$L_{eq(T)} = 10 \log_{10} \frac{1}{T} \int_0^T \left(\frac{p(t)}{p_{ref}} \right)^2 dt \quad (2)$$

Because it is an average no time weighting is applied. L_{Amax} is the maximum A-weighted noise level measured during the measurement time. It is vital to specify the time weighting. $L_{An,T}$ is the level of A-weighted noise that is exceeded n% of the measurement time. This parameter with n=90 is used as a measure of the background noise level. Time weighting, which is usually fast, should be stated. L_{DN} is the average day-night sound level. It is calculated from the L_{Aeq} with a 10 dB penalty for all noise occurring between 22:00 and 7:00, taking into account the increased annoyance at night. Additionally, the maximum sound pressure reached at any instant during a measurement period, L_{peak} , can be measured. This can be done using Z-weighting, but usually C-weighting is used. Because it is often found that single-number indices such as the L_{Aeq} do not fully represent the characteristics of the noise the frequency content can be measured in octave, 1/3 octave or narrower frequency bands. ^{65,66}

Each octave band is named for its center frequency. The range of human hearing of 20 Hz to 20 kHz can be divided into 10 octave bands, whose upper frequency band limit is twice the lower frequency

band limit. For more detailed frequency analysis the octave can be divided into smaller bands. The center frequencies for octave and 1/3 octave bands are shown in Table 3.

Table 3: Standard frequencies for acoustic measurements

Octave band center frequency	One-third octave band center frequencies
16 Hz	12.5 Hz, 16 Hz, 20 Hz
31.5 Hz	25 Hz, 31.5 Hz, 40 Hz
63 Hz	50 Hz, 63 Hz, 80 Hz
125 Hz	100 Hz, 125 Hz, 160 Hz
250 Hz	200 Hz, 250 Hz, 315 Hz
500 Hz	400 Hz, 500 Hz, 630 Hz
1000 Hz	800 Hz, 1000 Hz, 1250 Hz
2000 Hz	1600 Hz, 2000 Hz, 2500 Hz
4000 Hz	3150 Hz, 4000 Hz, 5000 Hz
8000 Hz	6300 Hz, 8000 Hz, 10000 Hz
16000 Hz	12500 Hz, 16000 Hz, 20000 Hz

3.5.1 Sources of noise in the ICU

High frequency noise up to 4 kHz is known to dominate the ICU ¹³. High noise levels can be created by a variety of sources in the ICU environment. In a study by MacKenzie et al. a total of 86 sources were identified ¹⁵. They determined the most dominant noise source for every 1 minute period based on the maximum SPL. The main sources of noise were waste bins (13.9%), general activity (13.2%) and talking (12.3%). A 24-hour recording analyzed by Park et al. showed that patient-involved noise accounted for 31% of the acoustic energy and the remaining energy was attributable for 57% to staff members, 30% to alarms and 13% to the operational noise of life-support devices.

3.5.2 Sleep disruption due to ICU noises

Buxton et al. conducted a study to determine the profiles of acoustic disruption of sleep caused by 14 sounds that are common in the hospital environment ⁶⁷. The sounds were administered at increasing decibel levels ranging from 40-70 dB(A) during specific sleep stages until an arousal response was observed. They found that electronic sounds, such as an intravenous pump alarm and a ringing phone were more arousing than other sounds, including human voices. Large differences were present in responses by sound type. Continuous stimuli are less arousing than intermittent stimuli. Further, sounds during N3 sleep were less likely to cause an arousal than sounds of a similar type and decibel level during N2 sleep.

CHAPTER FOUR

ANALYSIS OF SOUND IN THE ICU AND CORRELATION TO SLEEP IN PATIENTS

4.1 Introduction

As mentioned in previous chapters most ICU patients have severely disturbed sleeping patterns^{4,5,47,48}. The ICU is a very noisy environment and the environmental stimulus that is most often associated with disturbed sleep is noise^{11,12}. Previous studies have shown mean daytime noise levels of between 55-66 dB L_{Aeq} in patient rooms, with maximum levels of 80 dB L_{AFmax} . These high noise levels are caused by around the clock intensive treatment and the use of advanced technical equipment. Noise is often defined as sound that is unwanted or undesirable. It is a very complex phenomenon and by definition depends on how it is experienced, which depends on many parameters such as the sound level, nature of the sound and the subjective experience⁴³. However, most research on the effect of noise levels on sleep in hospital environments has focused solely on noise levels. The influence of other acoustic parameters such as the frequency spectrum is largely unknown in clinical populations⁴¹.

A few studies have also measured the frequency spectrum of noise in the ICU. Busch-Visniac et al. used octave bands and showed that low frequencies < 63 Hz had high sound levels, frequencies between 63 and 2000 Hz had medium sound levels and higher frequencies had low sound levels¹⁶. However, Ryherd et al.⁶⁸ and Darbyshire et al.¹³ used third-octave bands and concluded that ICU noise is dominated by high frequencies. This difference is likely caused by whether A-weighting is applied to approximate human hearing, since A-weighting is less sensitive to lower frequencies¹³. Darbyshire et al. were also able to identify some frequency components of the alarm noises. They found that the physiological monitors caused peaks in the 1.6-3.15 kHz bands for the normal alarms and in the 2.5-3.15 kHz bands for the more urgent alarms. The alarms of the infusion pumps were in the range of 800-1000 Hz while the ventilator alarms contained such a broad spread of frequencies that they could not be distinguished from other sounds¹³. However, in none of these papers the impact of the noise spectrum on patients' sleep was studied⁴¹.

From a study performed by Buxton et al. we know that different sound sources that are present in hospitals, each containing their own frequency bands, have different arousal probabilities⁶⁷. The aim of this study was to analyze the frequency spectrum of the sound in our ICU and investigate a possible correlation with sleep parameters in patients admitted to the ICU.

4.2 Methods

4.2.1 Subjects

Our institutional ethics committee approved the study protocol (registration number 2015.295). We included patients that were capable of giving informed consent, aged >18 years, expected to stay in the ICU 48h or longer, had a Richmond agitation and sedation score ≥ -3 and were capable of understanding and speaking Dutch. Patients were excluded if they had a pre-existing history or treatment of sleep pathology, severe visual or hearing impairment, alcohol addiction or illicit drug abuse, history of cognitive dysfunction (defined as dementia, traumatic brain injury, stroke or hepatic encephalopathy) or were admitted following neurosurgery. Written informed consent was obtained from each patient by dedicated research nurses.

4.2.2 Design

This observational study was undertaken in the ICU of the University Medical Center Groningen (UMCG). Upon enrollment, measurement equipment for monitoring sleep, activity, sound and light were set up according to a fixed protocol. Additionally, delirium was scored once every shift and blood samples were collected every 4 hours for melatonin concentration assessment. Other parameters recorded were ICU and hospital length of stay, mortality and amount of administered opioids, benzodiazepines, sedatives and antipsychotics. This report will focus solely on the data from the sound and sleep measurements.

4.2.3 Measurements

The quantity and quality of sleep can be measured objectively with PSG recordings, which is currently the gold standard for sleep measurement ⁹. For this measurement 6 EEG electrodes were placed on the scalp of the subject using the international 10-20 standard system (C3, C4, O1, F3, A1, A2). Also 2 EOG electrodes were placed near the top-right and bottom-left corners of the eye and an EMG electrode was placed on each jawbone.

For sound level monitoring an Earthworks M23 microphone (Earthworks, Milford, NH, USA), combined with Steinberg CL1 audio-to-PC interface and processing software, capable of storing the sound pressure level in real time, were used. The microphone meets ANSI Type 1 requirements and is capable of a flat frequency response up to 23 kHz. It was placed approximately 1m above the subjects head. With the distance of 1 meter the microphone does not disturb medical treatment, while still being close so that the sound is measured as much as possible as heard from the position of the patient. Also, the microphone should not be too close because then too much sounds caused by the patient him/her self are recorded. The A-weighted SPL was stored 42 times per second. The third octave bands for the frequency analysis were stored once every second. The time weighting was set to Fast for all measurements.

4.2.4 Analysis

In accordance with the WHO guidelines and ISO 1996-1:2016 day is defined as the 16 hour period between 7AM and 11PM and night as the 8 hour period between 11PM and 7 AM ^{69,70}.

The PSG data were sent to Philips Research Eindhoven for identification of sleep stages and arousals using the Somnolyzer 24x7 (Philips Respironics, Best, Netherlands) sleep scoring algorithm. Some PSG recordings were also already scored manually by a clinical neurophysiologist with significant experience in sleep staging. A comparison of the results of these two methods is shown in Appendix 1. Arousals were not scored manually. An arousal is defined as a wake period of between 3-15 seconds, after which sleep resumes, and is preceded by at least 10 seconds of stable sleep. This can be at the same sleep stage or at a different sleep stage.

Sleep and sound level data were then loaded into Matlab (Matlab 2014b, Natick, MA, USA) for further analysis. The sound level data and PSG analysis were synchronized using the timestamps of both recordings and outcomes were calculated for the day and night period. Mean sound levels per subject were calculated for L_{A90} , L_{Aeq} and L_{AFmax} . Also the number of events/h where L_{AFmax} was above 65 dB(A) and 75 dB(A), $\Delta dB \geq 10$ dB (which represents a doubling in sound intensity and is clearly audible) and $\Delta dB \geq 25$ dB were determined using the function findpeaks. The frequency spectrum was analyzed between 16 Hz and 8000 kHz. Finally, we determined which percentage of arousals was preceded by a sound peak in the 3 seconds before its occurrence.

4.3 Results

39 patients were included in this study giving a total of 1774 hours of data. Two patients were excluded: 1 because of technical problems and 1 because the patient decided to discontinue the study a few hours after the start of the measurements. Patients were 60.4 ± 10.5 years old and 51.4% were male. Data was collected from September 2015 until November 2016.

4.3.1 Sleep outcomes

The sleep characteristics calculated from the Somnolyzer sleep analysis algorithm are presented in Table . The average study inclusion was almost 2 days. Of this time a median value of 8.4 hours per day was spent asleep. Almost half of the sleep took place during the daytime between 7 AM and 23 PM. The number of sleep bouts was 2.4 during the day and 1.5 during the night. These sleep bouts had a median duration of only 1.5 to 2.4 minutes. Patients showed increased amounts of N1 sleep, a normal amount of N2 and N3 sleep and reduced amounts of REM sleep compared to normal values. The arousal index had a median of 13.3 arousals per hour, which is slightly below the normal values of 16.5-21.9 arousals per hour.

Table 4: Sleep characteristics as calculated by the Somnolyzer 24x7 algorithm (n=37)

	Median (IQR 25-75)	Normal values age 40-70 ^{69,71}
Duration of PSG recording, hours	47.3 (24.5-66.8)	
TST, hours	15.1 (9.9-30.5)	
TST per period of 24 hours, hours	8.4 (5.8-13.7)	6.5-6.8
Sleep during daytime hours, %	47.6 (31.7-60.1)	
Duration of sleep without waking day, min	1.5 (0.5-4.0)	
Duration of sleep without waking night, min	2.0 (0.5-5.5)	
Sleep periods day, no. per hour	2.4 (1.1-3.8)	
Sleep periods night, no. per hour	1.5 (1.1-2.3)	
N1, %	21.6 (13.0-34.2)	8-10
N2, %	53.8 (33.9-60.6)	55-57
N3, %	11.3 (2.1-26.9)	2-8
REM, %	1.2 (0.3-7.7)	8-10
Arousal-index, no. per hour	13.3 (8.7-17.9)	16.5-21.9

4.3.2 Sound outcomes

Background sound levels L_{A90} were slightly lower during the night than during the day, but the difference is very minimal and not significant (Table 5). The L_{Aeq} and L_{AFmax} were higher during the day. The L_{Aeq} during the day was almost 4 dB higher, which is substantial on a logarithmic scale. The increase in L_{AFmax} during the day is about 9 dB, which is almost a doubling of the maximum sound energy that is present at any one time during the measurement period. The spread of the sound levels per subject are also shown graphically in Figure 7. In Figure 8 the frequency content of L_{A90} , L_{Aeq} and L_{AFmax} during the day and during the night are presented. The background noise spectrum L_{A90} did not change over the day. For the L_{Aeq} one can see that there is more sound present for frequencies between 125 Hz and 4 kHz. For the L_{AFmax} the difference lies also in the sounds with frequencies above 125 Hz but the difference is most apparent above 1600 Hz. Figure 9 illustrates how the frequency spectrum shifts during the day in an example dataset, recorded during participation of patient 32. One can also see here that there is less sound pressure for higher frequencies during the

night. Also, a device producing mainly sound in the frequency range of 32-80 Hz was turned off from around 11 PM till 9 AM. In the high end of the spectrum something produced frequent spikes in the 3150 Hz frequency band, especially around 9 AM.

Table 5: Mean sound levels and occurrence of sound events in the ICU during the day and during the night (n=37) with P-value ($\alpha=0.05$) and confidence interval (CI, 95%)

Day		Night		P-value	CI
L_{A90}, 7AM-11PM, median (IQR)	42.7 (41.0-45.9)	L_{A90}, 11PM-7AM, median (IQR)	41.5 (38.9-44.7)	0.3118	-0.99-3.07
L_{Aeq}, 7AM-11PM, median (IQR)	54.3 (53.5-55.7)	L_{Aeq}, 11PM-7AM, median (IQR)	50.5 (49.0-52.0)	<0.0001	2.72-5.40
L_{AFmax}, 7AM-11PM, median (IQR)	100.4 (95.3-101.5)	L_{AFmax}, 11PM-7AM, median (IQR)	91.0 (88.0-100.1)	<0.0001	4.11-9.95
No. of events L_{AFmax} ≥ 65 dB(A) per hour, mean (sd)	755 (694)	No. of events L_{AFmax} ≥ 65 dB(A) per hour, mean (sd)	229 (238)	<0.0001	286-767
No. of events L_{AFmax} ≥ 75 dB(A) per hour, mean (sd)	69 (130)	No. of events L_{AFmax} ≥ 75 dB(A) per hour, mean (sd)	21 (30)	0.0308	4.6-91.8
No. of events ΔdB SPL ≥10 per hour, mean (sd)	1867 (673)	No. of events ΔdB SPL ≥ 10 per hour, mean (sd)	747 (409)	<0.0001	863-1379
No. of events ΔdB SPL ≥ 25 per hour, mean (sd)	131 (65)	No. of events ΔdB SPL ≥ 25 per hour, mean (sd)	50 (41)	<0.0001	55.6-105.7

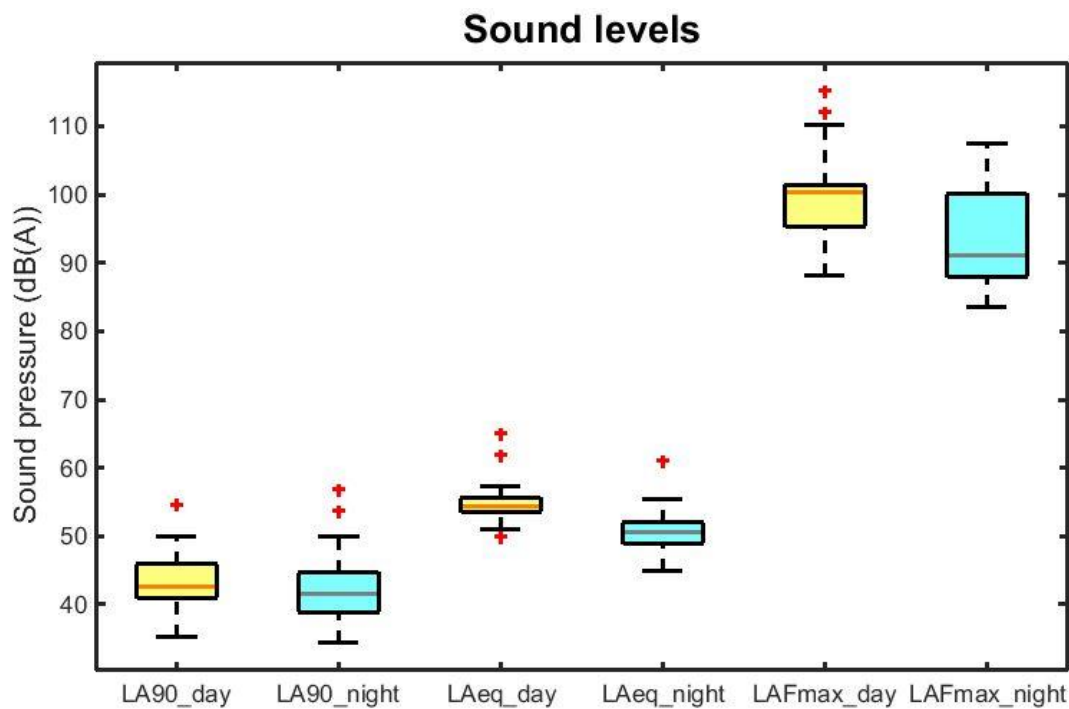


Figure 7: Distribution of sound levels in the ICU showing median (red line), 25 and 75 percentiles (colored box), range (black lines) and outliers (red +) for L_{A90}, L_{Aeq} and L_{AFmax}

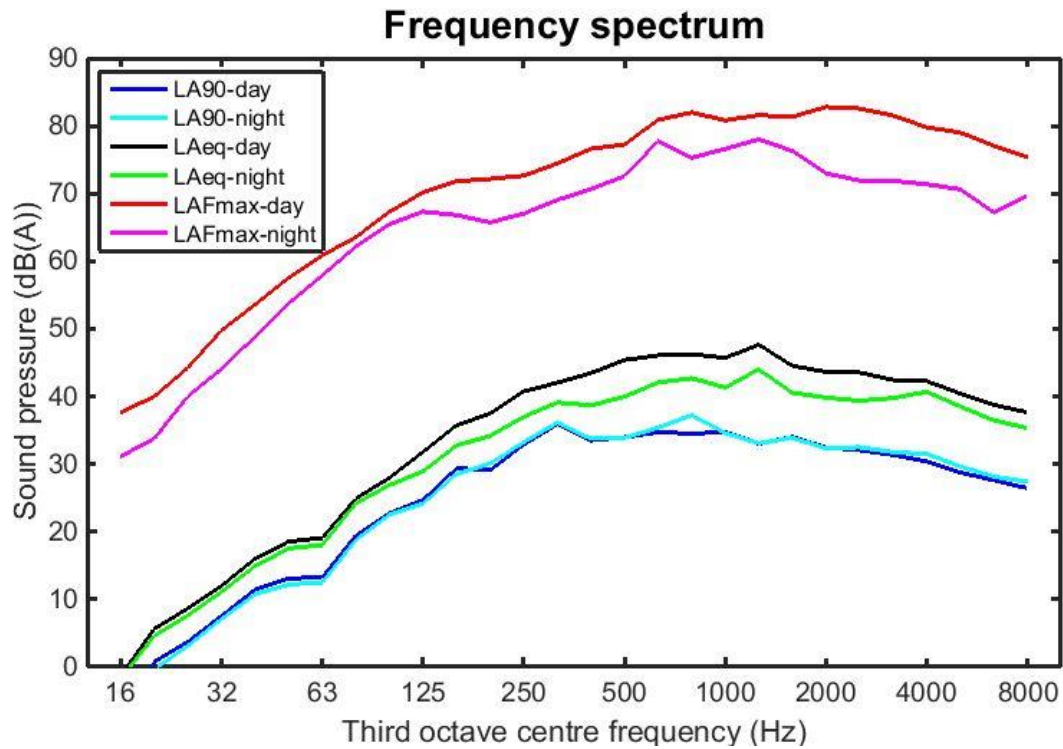


Figure 8: Frequency spectrum in the ICU during day and night for L_{A90} , L_{Aeq} and L_{AFmax}

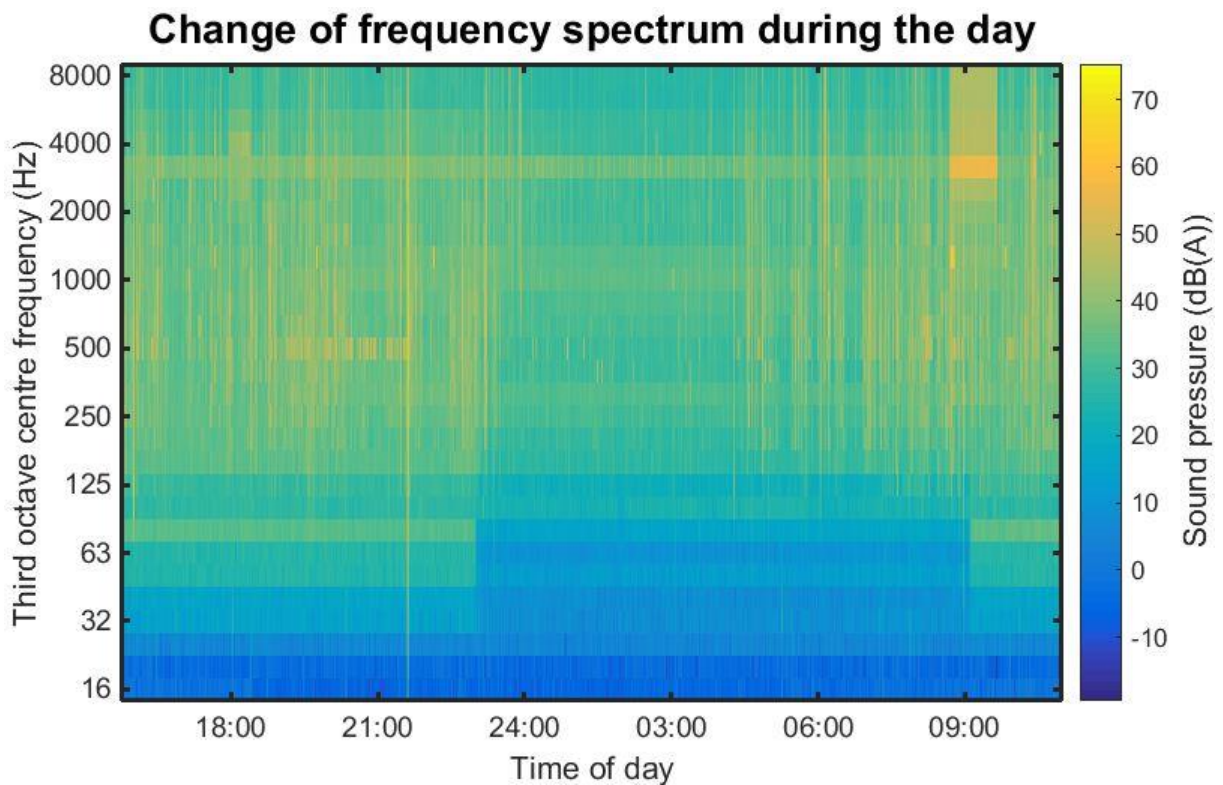


Figure 9: Frequency spectrum change during the day for the sound data of patient 32 with a window length of 1 second. The SPL for higher frequencies is lower during the night. In the 32-80 Hz range it is visible that a device was turned off around 11 PM and on again around 9 AM. In the high end of the spectrum something produced frequent spikes in the 3150 Hz frequency band (also during the night) and especially around 9 AM.

When looking at the distribution of local maxima with $\Delta\text{dB} \geq 10$ in the SPL over the frequency range, shown in Figure 10 it can be seen that there are more loud sounds in the range between 125 and 2000 Hz during the day and more above 2000 Hz during the night. For local maxima with $\Delta\text{dB} \geq 25$, also shown in Figure 10, this is the case between 400 and 2000 Hz during the day and around 3-4 kHz during the night.

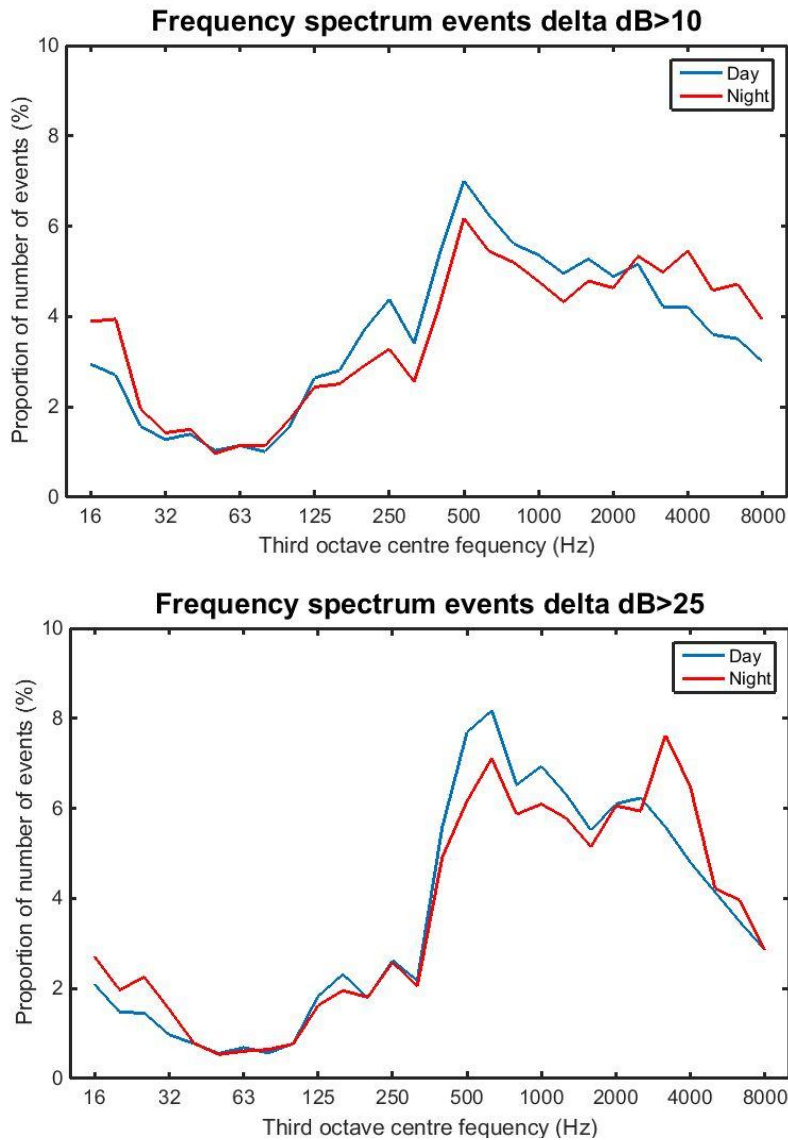


Figure 10: Frequency spectrum of maxima in SPL $\Delta\text{dB} \geq 10$ and $\Delta\text{dB} \geq 25$. For $\Delta\text{dB} \geq 10$ there are more loud sounds in the range between 125 and 2000 Hz during the day and more above 2000 Hz during the night. For $\Delta\text{dB} \geq 25$ there are more loud sounds between 400 and 2000 Hz during the day and around 3-4 kHz during the night.

Finally we also investigated the correlation between the occurrence of an arousal and the occurrence of a significant sound event, defined by a local maximum exceeding 65 or 75 dB(A) in the 3 seconds preceding the arousal. This correlation was $8.9\% \pm 6.2\%$ for arousals after an event with $\text{SPL} \geq 65$ dB(A) and $1.2\% \pm 1.1\%$ for arousals with $\text{SPL} \geq 75$ dB(A). However, we also have to take into account the random chance of such a maximum taking place in the 3 seconds preceding an arousal. The random chance of a sound event ≥ 65 dB(A) during this time window is $81.7 \pm 71.4\%$. An increase of sound events relative to the random chance of a sound event indicates an increased amount of stimuli. To determine if this was the case we divided the correlation by the random chance. If this

ratio is > 1 (Equation 3) this indicated causality, while when the ratio < 1 (Equation 4) the random chance is larger than the suggested correlation.

$$\frac{\text{Measured occurrence}}{\text{Chance occurrence}} > 1 \quad (3)$$

$$\frac{\text{Measured occurrence}}{\text{Chance occurrence}} < 1 \quad (4)$$

For sound events ≥ 65 dB(A) the average ratio was 0.13 (range 0.00-0.41). This means the random chance of such an event is about 8 times greater than that there is a causality. For events with $L_{AFmax} \geq 75$ dB(A) the average ratio is 0.24 (range 0.00-0.94).

4.4 Discussion

Although the sleep quantity of the subjects during their stay in the ICU was fairly normal (around 8 hours per day) it was very fragmented and about half of the sleep time was during daytime hours. The amount of N1 was increased while REM sleep was reduced. Similar findings are mentioned in other studies^{4,9,48}. The sleep was characterized by many sleep bouts with a very short median duration of only 1.5 minutes, which is even less than the median of 3 minutes previously found by Elliot et al.²⁷ Such short sleep bouts are believed to be too short for the restorative function of sleep to take effect⁵⁹. It is often mentioned in the literature that ICU patients also exhibit reduced SWS. A healthy percentage is said to be 20%⁹. However, according to values presented in a report by the WHO around 8% of stage 3 sleep is normal for adults aged 40-49 and around 2% for adults aged 60-69⁶⁹, which is the age range of the patients in this study. Because of this age range 20% SWS should not be expected.

The background sound level in the ICU is around 42 dB(A) and there is no clear difference between day and night. The equivalent sound level is on average 54 dB(A) during the day and 51 dB(A) during the night while the maximum sound level measured during the day was around 100 dB(A) and around 91 dB(A) during the night. These values match the levels found by Johansson et al.⁴³ of 51-55 dB L_{Aeq} and 82-101 dB L_{AFmax} and are slightly lower than those found by Ryherd et al.⁷² of 53-58 dB L_{Aeq} . Comparison with studies that measured sound and sleep is not possible, because a clear description of the measured sound parameters is often lacking.

We compared the spectral properties of noise in our measurements to those reported by Darbyshire et al.¹³ because they also applied A-weighting. Our measurements showed a roughly similar shaped frequency distribution. Sound levels for the middle frequencies are slightly lower in our data while the sound level of the high frequencies are higher and drop slower, for as far as a comparison is possible with our analyses being cut off at 8 kHz. However, the most noticeable difference is that the noise levels for frequencies below 125 Hz were much lower in our measurements. Like Darbyshire et al. we also noticed a reduction in sound levels predominantly above 400 Hz. The cause for this is that lower frequency sounds are caused by hospital systems and other factors that are always present and do not show diurnal variation. The higher frequencies by contrast are caused by conversations, alarms etcetera that decrease at night.

We calculated the number of events where $L_{AFmax} \geq 75$ dB and $\Delta dB \text{ SPL} > 10$ so that they could be compared to the results from Gabor et al.²⁵ and Stanchina et al.³⁴. Gabor et al. found 9.5 ± 6.8 peaks > 75 dB/h during wake periods and 1.7 ± 1.5 during sleep periods in an open ICU in the part of their study investigating patients. We assume that they used A-weighting for their measurements and

mean 75 dB(A). This is not clearly stated in the paper. They also observed 37 sound peaks/h of sleep with an increase of more than 10 dB. They were able to link $30.8 \pm 17.9\%$ of arousals and awakenings to these peaks > 75 dB and 12-20% of noise increases of more than 10 dB. In our study there were 69 ± 130 events where $L_{AFmax} \geq 75$ dB(A) during the day and 21 ± 30 events during the night. For the increases in SPL > 10 dB there were almost 2000 events during the daytime and around 800 event during the nighttime. So for both parameters our values are a lot higher. We can only speculate about the reason for this. It might have something to do with the noisiness in the ICU but it is also possible that it is caused by different settings of the measuring equipment. However, we were only able to correlate $1.2\% \pm 1.1\%$ of the arousals to a sound event with $L_{AFmax} \geq 75$ dB(A) and determined that this correlation was purely based on chance occurrences. The correlation for $\Delta dB \geq 10$ was larger but with events occurring with less than 2 seconds apart this was also based on chance. Because we did not find a relation between noise events and arousals it also was not possible to determine the effect of sounds in individual frequency bands.

4.4.1 Limitations of the study

We chose to include as much data as possible, meaning that we not only analyzed data from whole 24 hour periods but rather used all data from patients that were in the study for at least 16 hours. Because the aim of this study was to analyze the frequency spectrum of the sound and the correlation between sound events and sleep parameters, it was not vital to have complete 24 hour datasets. This may however have had some influence on the sleep parameters, particularly the distribution of sleep over day and night. The results for our study do however correspond to results from other studies. It may also have had a small influence on the measured sound levels and events during the daytime period (patients did not leave the study during the night).

Further, sleep stages and arousals were not manually scored by an experienced neurologist but by a computer algorithm. The Somnolyzer algorithm is a clinically validated scoring system which uses the same scoring rules a human expert would. However, the traditional sleep scoring criteria are often not uniformly applicable in critically ill patients^{8,50}. Also, because scoring is performed per epoch of 30 seconds it is not possible to determine the precise time of an awakening for comparison with sound events, although arousals were scored and individually labeled independently from epoch definitions.

Also, it is possible that because the microphone was so close to the patient a substantial amount of the recorded sound originates from the patient him/herself. To resolve this it would be necessary to use at least 2 measuring locations at different distances relative to the patient.

Finally, we did not test patients hearing capabilities, while age-related hearing loss is common at the age of most of the patients included in this study.

4.5 Conclusion

The results from this study are in accordance with previous ICU sleep research. Our patients showed severely fragmented sleep with reduced REM activity. The reduction in stage 3 sleep seems to be less evident when compared to normal values in the same age group. The number of events where sound pressure suddenly increased twofold, or even more, was a lot higher than described in other studies. The reason for this is unknown. We were not able to correlate sound events to arousals, due to an overabundance of chance occurrence of sound events in particular. Future research should study healthy volunteers in the active ICU environment and have a human expert score the sleep stages

and arousals and awakenings. This way the underlying sleep pattern and characteristics will be relatively normal and therefore much easier to assess. Furthermore, all disturbance of sleep will be caused by the environment and not by factors related to illness.

CHAPTER FIVE

CONTRIBUTION OF THE ICU ENVIRONMENT TO SLEEP DISRUPTION IN HEALTHY SUBJECTS

5.1 Introduction

Studying the primary effects of the busy ICU environment is complicated in patients, as we have shown in our review in chapter 2. First of all, it will be unclear whether intrinsic or extrinsic factors are most important. Ventilator interactions, underlying illness, medications, nursing interventions, and the environment will all contribute to sleep disruption³⁴, making it extremely hard to determine the relative effect of each individual factor^{18,41,73}. To complicate matters even further a nursing intervention or for example patient/ventilator asynchrony may trigger an alarm, which may lead to arousals or awakenings to be registered as being caused by a sound peak when in fact it was caused by the event triggering the alarm⁴⁸. Secondly, as discussed in chapter 3, EEG recordings in ICU patients are challenging to interpret because of altered EEG patterns, that hamper sleep staging in accordance with the R&K sleep scoring rules^{6,33,36,73}.

Studying the primary effects of the busy ICU environment can therefore best be done in a more homogenous and controllable group of healthy volunteers. A study by Stanchina et al.³⁴ used a simulated ICU environment to study the isolated effects of recorded ICU sound on 5 healthy subjects. In this study 63% of the observed arousals could be related to peaks in sound. In other studies regarding sleep in healthy subjects in a simulated ICU environment, sound was often (partly) modified to study the effect of this modification^{33,34}, or the correlation between arousals and sound peaks was not investigated at all³².

Although simulating the ICU environment is very suitable to study interventions in the sound environment, the results cannot plainly be extrapolated to a real ICU environment³⁶. The acoustic characteristics in ICUs are caused by multiple complicated and dynamic noise sources⁴¹. The playback of noise through speakers may lead to greater sleep disruption caused by magnification of the sound effect³⁴, as has been shown in this review by Pearsons et al.⁷⁴, which found large differences in sleep disturbance between laboratory and field settings in other noisy environments. Further, sound and noise are very complex phenomena and the meaning of the sound, among other factors, is also critical for the amount of disturbance^{11,43}. This suggests that recorded ICU noise might have a smaller effect on sleep disturbance because of the different subjective experience. Furthermore, disturbed sleep is often experienced in environments that are new to the sleeper⁷⁵. This effect may be expected to be larger in a real ICU compared to a simulated environment.

Gabor et al.²⁵ placed 6 healthy subjects between critically ill patients in an active ICU. They could relate 69% of arousals and 58% of awakenings to peaks in sound when the subjects lay in an open ICU. In a single room, sound was deemed responsible for 47% and 37% of arousals and awakenings, respectively. This suggests that in healthy subjects noise is responsible for the majority of sleep disruptions.

The first step in getting a better understanding of the relation between sleep and the ICU environment is to analyse the isolated effects of the sensory stress that accompanies admission to the ICU. By studying healthy subjects' sleep in an active ICU environment, the relative importance of the environment in the disturbance of sleep can be determined. Several studies have attempted to

simulate the experience of being admitted to an ICU, but none have been able to replicate the full multi-sensory experience ³². To our knowledge only one small study has ever investigated the influence of an actual ICU on healthy subjects' sleep. Therefore more data is needed to get a better understanding about the effect of the ICU environment on people. Particularly the analysis of the noise present in the ICU should be done more thoroughly ⁴¹.

Primarily, this study will investigate the role of sound, light and the inherent experience of the ICU environment on the incidence of arousals, and therefore the continuity of sleep. Focusing on the study of healthy subjects eliminates confounding and immeasurable intrinsic factors present in patients that may interfere with clear analysis of this relation.

5.2 Methods

5.2.1 Subjects

Our institutional ethics committee approved the study protocol (registration number 2016.632). Subjects meeting the following criteria were included: healthy adult (age ≥ 18 years) nurses and doctors (in training) that were not working in the ICU at the time of the study and had normal hearing. Hearing abilities were tested using the Dutch National Hearing Test, which is a validated and easy to perform speech-in-noise test ⁷⁶. Exclusion criteria were: pre-existing history or treatment of sleep pathology, use of sleep promoting medication and alcohol addiction or illicit drug abuse. Subjects were asked to abstain from consuming alcohol on the day before PSG measurements and abstain from caffeine consumption after 12 AM before a measurement, because these substances are known to interfere with normal sleep ^{77,78}.

5.2.2 Design

During this prospective repeated measures study, healthy subjects were exposed to different sleep environments including an operational ICU. It is designed to examine two main areas of interest: quality of sleep and the sensory environment of the ICU patient. The environmental factors that will be measured are sound, light and temperature.

Subjects were monitored during 2 study nights: home and active ICU. The subjects first slept one night at home with PSG as a baseline measurement for the subject's sleep architecture. Next, one night was spent in an active ICU. During the night in the active ICU subjects slept on the ward between ICU patients. We used a bed space that is in the middle corner of an L-shaped ward, which is never used to admit patients because of lack of space around the bed. To prevent acclimatization there was a minimum three day interval between the study nights.

5.2.3 Measurements

During the Home and ICU nights, sleep quality, quantity and distribution were measured using PSG. The electrodes necessary for PSG were placed on the scalp of the subject using a special adhesive according to the international 10-20 standard system: F3, A1, A2, C3, C4, O1, ground and reference. Together with these EEG electrodes two EOG electrodes were placed on the left-top and right-bottom near the eye. Two EMG electrodes were placed on the jaw muscles according to normal protocol.

For sound level monitoring at home the Vital Minds ICU sound and light measurements app (Philips, Best, Netherlands) for the Samsung Galaxy S3 Neo smartphone was used. For sound level monitoring

in the ICU an Earthworks M23 microphone (Earthworks, Milford, NH, USA), combined with Steinberg CL1 (Steinberg Media Technologies GmbH, Hamburg, Germany) audio-to-PC interface and processing software, capable of storing the sound pressure level in real time, were used. The microphone meets ANSI Type 1 requirements and is capable of a flat frequency response up to 23 kHz. It was placed approximately 1m above the subjects head. The A-weighted sound pressure level (SPL) and third octave bands were stored 18 times per second. The time weighting was set to Fast for all measurements.

For illuminance and irradiance measurements, an Actiwatch Spectrum was used. The normally wrist worn device will be placed near the bedhead and monitors light intensity of 3 major spectral bands (red, green and blue) and total light intensity during the study period. For temperature measurements the Ebro EBI 300 digital environmental USB-temperature logger (Ebro Electronic GmbH, Ingolstadt, Germany) was used.

5.2.4 Analysis

Sleep stages and arousals were determined by the Somnolyzer 24x7 (Philips Respironics, Best, Netherlands) sleep scoring algorithm. An arousal is defined as a wake period lasting between 3-15 seconds, after which sleep resumes. An arousal needs to be preceded by at least 10 seconds of stable sleep. This can be at the same sleep stage or at a different sleep stage.

Sleep and sound level data were loaded into Matlab (Matlab 2014b, Natick, MA, USA) for further analysis. Only the data from the time of sleep onset until wake was analyzed. The sound level data from the ICU and PSG analysis were synchronized using the timestamps of both recordings and outcomes were calculated. Mean sound levels per subject were calculated for L_{A90} , L_{Aeq} and L_{AFmax} . Also the number of sound events per hour above 65 dB(A) and 75 dB(A) were determined using the findpeaks function. The frequency spectrum was analyzed between 50 Hz and 8 kHz. Finally it was determined which percentage of arousals was preceded by a sound peak in the 3 seconds before its occurrence. L_{Aeq} and L_{AFmax} were calculated from the sound level recording from the home condition for the period that the subject was in bed. The data from the light measurements were viewed in Respironics Actiware 5 (Philips Respironics, Best, Netherlands). Because the measured illuminance levels were constant most of the time the value from one representative measurement point was read. The data from the temperature logger was read into Excel 2010 (Microsoft, Redmond, WA, USA) to calculate the average temperature for the period that the subject was in bed.

5.3 Results

Thus far 3 subjects that have been included in the study have completed both the home and ICU measurements. Measurements all took place in February 2017. Subjects were all females aged 37.0 ± 15.6 years with normal hearing. The outcomes from the sleep analysis are shown in Table 6. Subject 1 and subject 3 show reduced sleep quality in the ICU compared to at home while subject 2 slept better in the ICU. The outcomes from the analysis of the environment are shown in Table 7. The background noise level in the ICU was 40.0 dB(A), the L_{Aeq} was around 43.8 dB(A) and the L_{AFmax} was around 84.3 dB(A). Increases in sound level above 65 dB(A) occurred around 20.6 times per hour and increases above 75 dB(A) occurred around 1.6 times per hour. Sound levels at home were lower than in the ICU. Light exposure was not an issue either at home or in the ICU with light levels below 1 lux for the majority of the time. However, there was a big difference in temperature between the subjects home and the ICU. At their homes the temperature was on average 13.0°C, while it was

23.3°C in the ICU. The temperature data for the ICU measurement from subject 2 are missing because of a technical problem. The sleep pattern (hypnogram) and SPL for the ICU night are plotted together for each subject in Figure 11.

Table 6: Sleep characteristics as calculated by the Somnolyzer 24x7 algorithm

	Subject 1		Subject 2		Subject 3		Mean (sd)	
	Home	ICU	Home	ICU	Home	ICU	Home	ICU
TST, hours	5.1	7.2	3.6	5.7	8.1	5.8	5.6 (1.9)	6.2 (0.7)
N1, %	5.3	6.2	8.6	9.0	5.4	3.8	6.4 (1.5)	6.3 (2.1)
N2, %	53.5	68.4	75.2	62.6	57.4	72.6	62.1 (9.4)	67.9 (4.1)
N3, %	28.2	12.4	9.3	15.6	23.1	19.0	20.2 (8.0)	15.6 (2.7)
REM, %	13.0	13.0	6.9	12.8	14.1	4.6	11.3 (3.1)	10.2 (3.9)
Arousal-index, no. per hour	14.2	23.7	16.1	7.7	8.4	9.2	12.9 (3.3)	13.5 (7.2)
Duration of sleep without waking, min	9.5	18.5	6.9	10.7	15.2	11.3	10.5 (3.5)	13.5 (3.5)
Sleep periods, no. per hour	4.2	2.9	3.7	4.5	3.5	4.6	3.8 (0.3)	4.0 (0.8)

Table 7: Mean sound levels, occurrence of sound events, light exposure and temperature at home and in the ICU during the night

	Subject 1		Subject 2		Subject 3		Mean (sd)	
	Home	ICU	Home	ICU	Home	ICU	Home	ICU
L_{A90}, night	-	40.2	-	40.1	-	39.7	-	-
L_{Aeq}, night	38.5	44.4	36.2	43.0	41.2	43.9	-	-
L_{AFmax}, night	79.4	86.0	76.8	84.6	81.7	82.4	-	-
Max ≥ 65 dB(A) per hour	-	34.9	-	8.0	-	19.0	-	20.6 (11.0)
Max ≥ 75 dB(A) per hour	-	2.4	-	0.3	-	2.2	-	1.6 (0.9)
Light, lux	0.0	0.1	0.0	0.5	0.0	0.0	0.0 (0.0)	0.2 (0.2)
Temperature, °C	13.4	23.0	17.5	-	8.2	24.0	13.0 (3.8)	23.5 (0.5)

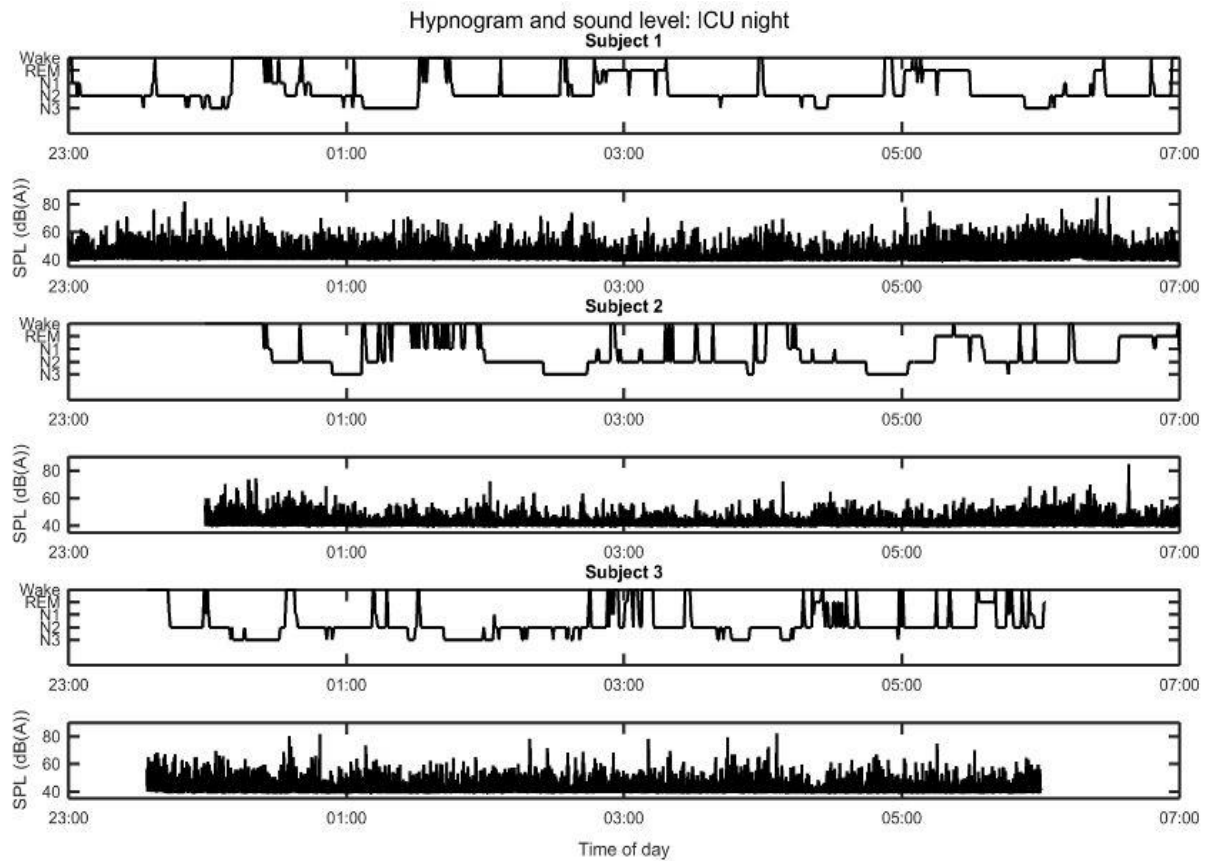


Figure 11: Hypnogram and SPL for each subject for the ICU night

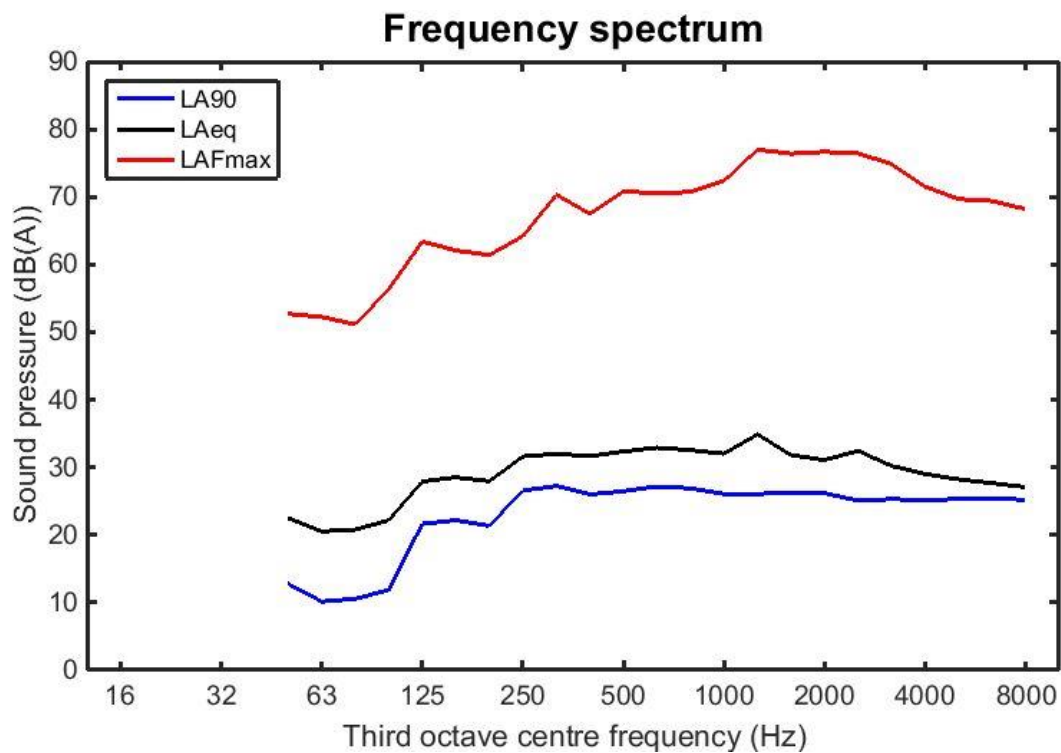


Figure 12: Frequency spectrum in the ICU during the night for L_{A90} , L_{Aeq} and L_{AFmax} . There are no values for frequencies below 50 Hz because these could not be calculated at a rate of 18 samples per second.

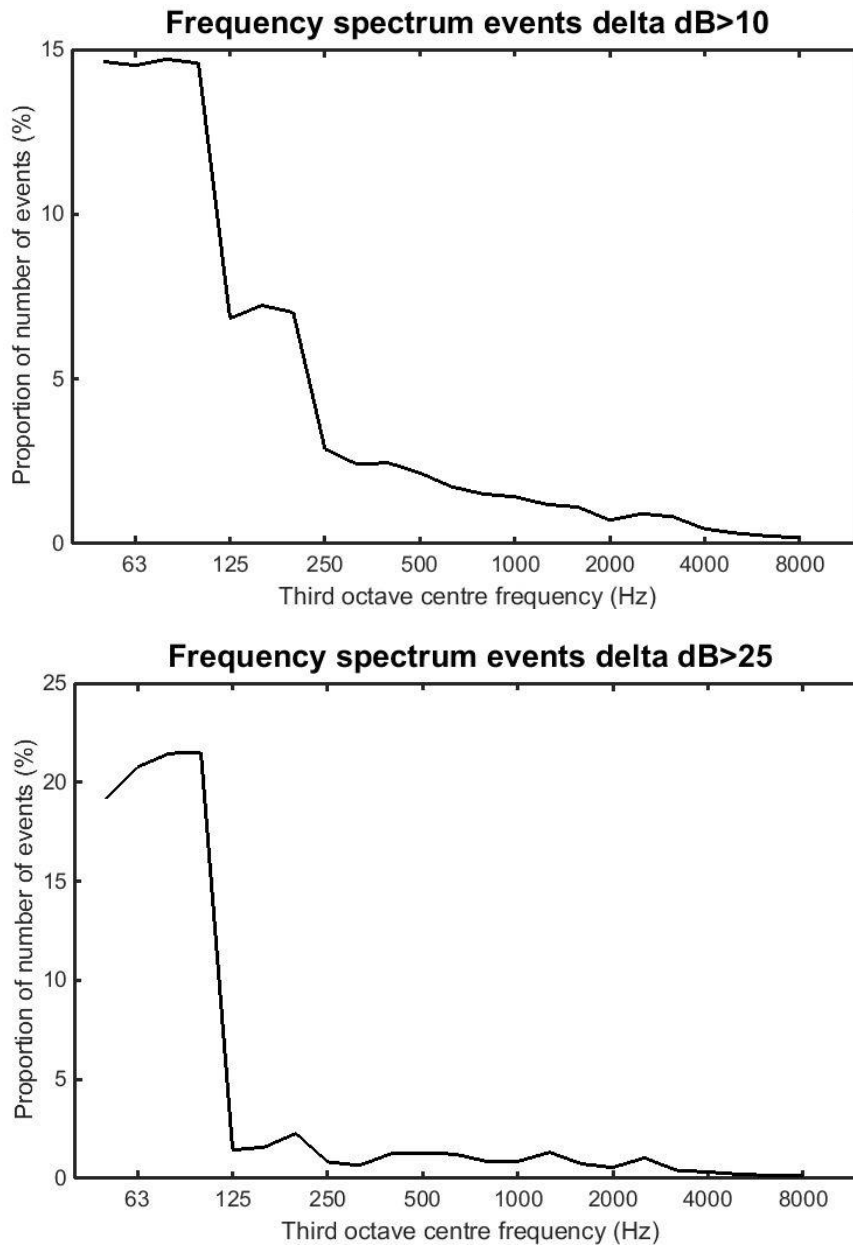


Figure 13: Frequency spectrum of maxima in SPL $\Delta\text{dB} \geq 10$ and $\Delta\text{dB} \geq 25$ for frequency bands 50 Hz – 8 kHz

The frequency spectrum, shown in Figure 12, of the background (L_{A90}) and equivalent noise levels (L_{Aeq}) is mostly flat from 125 Hz upwards. There is a small peak in the spectrum of the L_{Aeq} at 1250 Hz and a gradual roll-off above 2.5 kHz. The L_{AFmax} shows the loudest sounds for higher frequencies above 1 kHz.

The frequency distribution of sound events is shown in Figure 13. It is clear that most sound events are in the lower frequency bands. Most events, both with $\Delta\text{dB} \geq 10$ and $\Delta\text{dB} \geq 25$, are below 125 Hz. For $\Delta\text{dB} \geq 10$ there are also many events between 125 and 250 Hz. However, these low frequency sounds are at very low decibel levels of below 20 dB(A). When we look at the spectrum from 125 Hz up for events with $\Delta\text{dB} \geq 25$ we get the distribution shown in Figure 14. We see then that besides a peak at 200 Hz, also sounds with frequencies around 500, 1250 and 2500 Hz are present more frequently.

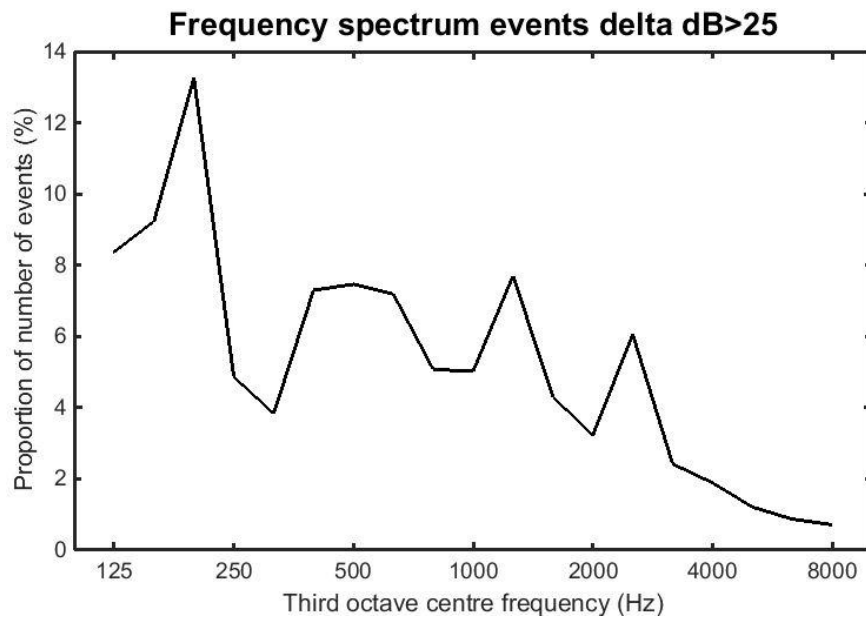


Figure 14: Frequency spectrum of maxima in SPL Δ dB \geq 25 for frequency bands \geq 125 Hz

There was no correlation between the occurrence of an arousal and the occurrence of a sound event in the 3 seconds preceding the arousal.

5.4 Discussion

We have shown that 2 out of 3 healthy subjects experienced reduced sleep quality in the ICU compared to at home. The third subject slept better in the ICU than at home. There were large differences observed between the subjects for all sleep parameters. Since the home measurement was the first experience for the subjects with the sleep study equipment. Therefore it is possible that their sleep was affected because they had to get used to the equipment. Background, equivalent and maximum sound levels in the ICU were lower than previously measured in the patient study described in chapter 4. The frequency spectrum was more flat for the background and equivalent level, while it was similar to our previous measurements for the L_{AFmax} . In this study we also measured far more sound events in the low frequency bands. This is probably caused by the higher sample frequency used here of 18 samples/sec versus 1 sample/sec in the patient study. Because the sound level is very low at these low frequencies they are not very important. It would be interesting to know which sound sources are responsible for the increase in sound events around 500, 1250 and 2500 Hz. These are most likely speech, whose maximum energy is in the 250-500 Hz range, and alarm sounds. The number of sound events where $L_{AFmax} \geq 65$ dB and $L_{AFmax} \geq 75$ dB were also a lot lower than in the patient study (21 vs 229 and 2 vs 21 events/h). This is probably due to the larger distance to the sources of these loud sounds. There were no monitoring or other systems active at the bedside of the healthy subjects. Also no ICU-staff activity near the bed occurred. This apparently has a significant impact on the occurrence of loud sounds. No increase in the amount of light at the bed was measured during this study. This will be different for patients because they frequently require check-ups and care from the staff. Still, it could not have been a sleep disruptive factor for our subjects. The temperature on the other hand might have played a role in sleep comfort because the temperature in the ICU (23.5 °C) was a lot higher than at the subjects homes (13.0 °C). Thermal comfort is known to be important in human sleep⁷⁹. Sleep time and sleep efficiency increase when sleeping in a room with a lower temperature⁸⁰. Some studies also reported a larger amount of REM

and SWS⁸⁰. No correlation between sound events and arousals was found. This is remarkable, because previous studies have shown that up to 68% of arousals in healthy volunteers in an open ICU was caused by sound^{25,34}. The sound data should be analyzed further and also other aspects than the 3 second window before an arousal should be investigated.

5.4.1 Limitations of the study

These are preliminary results from a very small number of subjects, which made it difficult to interpret the results. The goal is to eventually include 10 subjects into this study. It also was not possible yet to perform measurements in a quiet ICU environment. These are going to take place over the next months. The study protocol with a description of all additional data that will be gathered is available in Appendix 2. With the addition of these measurements it will be possible to quantify the 'first-night' effect, which is present when a person sleeps in an unfamiliar environment and has a negative influence on sleep quality. Also this will be a much more controlled measurement environment than the subject's home. There will be no sleep disturbance due to children, pets or other factors that might be present at home, the temperature will resemble that of the active ICU and we will be able to monitor the sound levels and spectrum in the same way as in the active ICU. This will make it easier to compare the results. Further, sleep scoring should be checked by a human expert to get the most reliable results and detailed information on arousals and awakenings. So far this has been done for 2 recordings. The results are presented in Appendix 1.

5.5 Conclusion

Thus far we have found that 2 subjects had worse sleep quality in the ICU, while 1 subject slept worse at home. Sound levels were much lower than in the patient study described in chapter 4. We were not able to correlate any arousals to sound events. We also found a significant difference in ambient temperature which might have influenced sleep quality. More subjects need to be included and more detailed and manual analysis of the sleep data is necessary. Also the analysis of the sound data should be extended so that we get more information on the relation between sound and sleep. Finally, the sleep data should also be assessed manually to verify the identification of sleep stages and to get more detailed information on arousals and awakenings. For future research it might be important to make sure that the noise levels experienced by healthy subjects are similar to those experienced by patients.

CHAPTER SIX

GENERAL DISCUSSION AND RECOMMENTATIONS

In this report the contribution of sound in the ICU environment to sleep disruption in patients and healthy volunteers was investigated. Results from the review indicate that ICU noise might have a negative effect on sleep quality in healthy volunteers. It was not possible to determine this for patients, because it is not possible to measure under baseline conditions in this population. However, it has also been shown that a lot of questions can be raised regarding the literature that is available on this topic. Most studies included only small sample sizes. Further, special attention needs to be given to complete and correct execution of sound measurements. Most published literature on hospital noise has been written by medical specialists who often have insufficient knowledge about acoustics¹⁶. This has led to incorrect computing of parameters and inconsistent or lacking specification of the measurement settings such as frequency and time weighing^{16,81}. Secondly, the results regarding sleep and noise from our study in ICU patients were in accordance with previous research by other groups. Sleep was fragmented with reduced REM activity. However, the number of sound events was a lot higher than previously described in the literature. We were not able to relate these sound events to arousals. Finally, we investigated sleep in the ICU environment in healthy volunteers because sleep disruption in ICU patients is very multifactorial and there are many confounders that one cannot correct for. Thus far only a very small number of 3 subjects had completed the home and ICU measurements. 2 subjects slept worse in the ICU while 1 slept worse at home. We were able to determine that the sound levels were a lot lower in this study, due to the added distance to ICU monitoring and treatment devices and staff activity. Here we were also not able to correlate any arousals to sound events.

6.1.1 Recommendations for future research

The variation in study protocols and lack of adequate reporting on acoustic parameters and settings make it very difficult to compare results. Further, sleep disruption in ICU patients is multifactorial which makes it very difficult to differentiate causes. The problem with the conventional sleep scoring criteria in critically ill patients only adds to this problem. The most important aspects regarding future research are summarized below:

- The contribution of the ICU environment to sleep disruption should be investigated in the real ICU environment in healthy volunteers. They show normal EEG sleep stage characteristics and can be measured under various conditions for comparison.
- Care should be taken to ensure correct reporting of acoustic parameters and settings, so that results are comparable across studies.
- Although most research is focused only on sound levels, other acoustic parameters such as frequency spectrum, reverberation time, nature of the sound and the difference of the sound levels with the background sound levels are also important to determine the comfort of the acoustic environment.
- Ultimately it would be very interesting to determine the most important causes of noise in the ICU and for sleep disruption caused by noise. To achieve this high resolution frequency data is needed, since many noise sources in the ICU environment such as alarms have a very short duration. To do this it would be best if the audio signal could be recorded. Although it sounds easy this is difficult to execute. Park et al.⁸² have done this and analyzed the

soundscape in the ICU based on the annotation of an audio recording. They made a continuous recording in a single patient room over a period of about 3 days. During this period they obtained informed consent from all persons who entered the room, including patients, visitors and staff. Next the recording was annotated off-line by a team of 6 research assistants who needed about 350 hours for this task. Obtaining informed consent from every person present is not an option in our open plan ICU. Further this method is not suitable for studies with more than a few days of measurement time. An alternative is to place an observer in the space to write down the sources of sounds. This approach was used by MacKenzie et al.¹⁵ who had an observer identify the events causing the maximum noise levels for every minute. This method is not as precise and another problem is the Hawthorne effect, i.e. the presence of the observer influences the environment of situation examined.

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APPENDICES

Appendix 1: Comparison Somnolyzer and manual sleep scoring

Table 1: Comparison between Somnolyzer and manual sleep scoring in data from PSG measurements in 7 ICU patients shown as median (IQR). Differences are most prominent in the number of sleep periods where Somnolyzer shows more fragmented sleep and in the amount of N1 and N2 sleep. The manual scorer almost never scored N1 because this stage is very difficult to identify in recordings from ICU patients.

	Somnolyzer	Manual
Duration of PSG recording, hours	46.1 (43.5-70.3)	46.1 (35.8-69.2)
TST, hours	15.1 (10.1-35.7)	19.5 (10.0-32.3)
TST per period of 24 hours, hours	6.4 (5.3-12.8)	7.9 (6.7-11.7)
Sleep during daytime hours, %	41.6 (20.8-58.1)	38.2 (17.9-57.9)
Duration of sleep without waking, min	1.5 (0.5-4)	3.5 (1.5-10)
Number of sleep periods	78 (52-188)	62 (19-79)
Stage 1, %	13.9 (12.0-20.8)	0.3 (0.2-2.0)
Stage 2, %	47.4 (29.5-61.2)	81.4 (59.7-85.3)
Stage 3, %	37.9 (19.0-49.5)	18.0 (13.3-37.4)
REM, %	0.9 (0.5-4.8)	1.1 (0.0-2.8)

Table 2: Comparison between Somnolyzer and manual sleep scoring in data from PSG measurements in 2 healthy subjects in the ICU shown as median (IQR). More information on sleep stages is presented in Figure 1 and Figure 2.

	Subject 1		Subject 3	
	Somnolyzer	Manual	Somnolyzer	Manual
TST, hours	7.2	6.9	5.8	6.5
Duration of sleep without waking, min	18.5	21.4	11.3	25.5
Number of sleep periods per hour	2.9	2.0	4.6	1.7
Stage 1, %	6.2	0.4	3.8	1.3
Stage 2, %	68.4	65.0	72.6	51.3
Stage 3, %	12.4	21.0	19.0	24.5
REM, %	13.0	13.6	4.6	22.9

The ICU recording from subject 3 was also manually scored for arousals and awakenings. 10 arousals and 14 awakenings were identified of which 9 (total) were also identified by Somnolyzer (Somnolyzer identified a total of 89 arousals). However, it was still not possible to correlate these manually scored EEG events to sound events. A factor that might play a role in this is that it was discovered that the sample rate of the sound recording software was not constantly 18 samples/second. With subject 1 it was 17.6 samples/second on average (for subject 2 it was around 17.95 and for subject 3 it was around 17.9).

Healthy subject 1

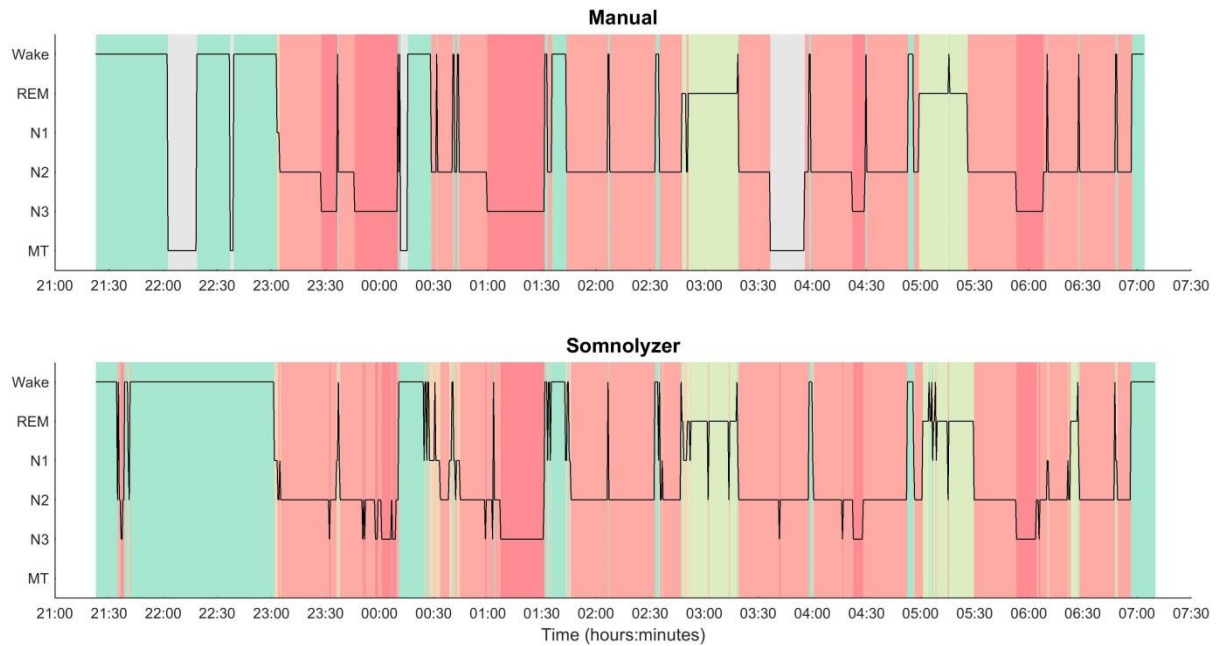


Figure 1: Comparison between Somnolyzer and manual sleep scoring. Wake = green, REM = yellow, N1 = peach, N2 = light red, N3 is dark red and grey = movement time (MT). Movement time was scored when the headbox was disconnected from the measurement computer. Although there are some differences the general sleep pattern is similar. What stands out the most is that the period between 3:30 and 4:00 scored as MT in the manual scoring, is scored as N2 by Somnolyzer.

Healthy subject 3

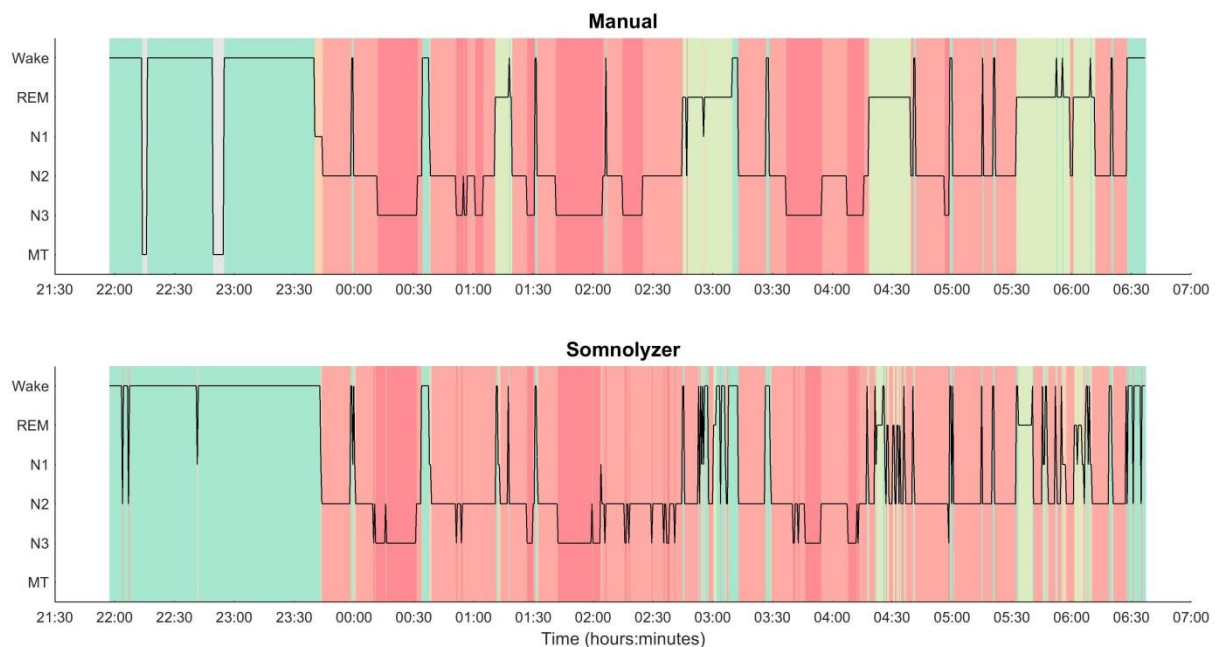


Figure 2: Comparison between Somnolyzer and manual sleep scoring. Wake = green, REM = yellow, N1 = peach, N2 = light red, N3 is dark red and grey = movement time (MT). Movement time was scored when the headbox was disconnected from the measurement computer. In this measurement also the general sleep pattern is similar. Here the most prominent differences are with the scoring of REM. Much more REM was scored manually than with Somnolyzer.

Appendix 2: Research Protocol for METc

RESEARCH PROTOCOL

CONTRIBUTION OF THE INTENSIVE CARE UNIT ENVIRONMENT TO SLEEP DISRUPTION IN HEALTHY SUBJECTS

Protocol ID	Sponsor: 2015-0100 UMCG research register: 201600632 ABR: NL58334.042.16
Short title	Sleep ICU healthy subjects
Version	1.3
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
ADE	Adverse Device Effect
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
EEG	Electro-encephalography
KSS	Karolinska Sleepiness Scale
IB	Investigator's Brochure
IC	Informed Consent
ICU	Intensive Care Unit
METC	Medical Research Ethics Committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NREM	Non-Rapid Eye Movement
PSG	Polysomnography
R&K	Rechtschaffen & Kales
REM	Rapid Eye Movement
RSCQ	Richards-Campbell Sleep Questionnaire
(S)AE	(Serious) Adverse Event
SPFS	Samn-Perelli Fatigue Scale
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SWS	Slow Wave Sleep
TST	Total Sleep Time
UMCG	University Medical Center Groningen
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Patients admitted to an intensive care unit (ICU) are exposed to several intrinsic and extrinsic sleep disruptive factors, causing disturbed sleep, which may have detrimental effects on patient cognition and behaviour. Because so many factors play a role, studying the primary effects of the busy ICU environment is complicated in patients and can therefore best be done in healthy volunteers.

Primary objective: To investigate the correlation between stressors present in the ICU environment and continuity of sleep, in healthy subjects.

Secondary objective: To determine the quality, quantity and distribution of sleep in healthy subjects in different environments.

Study design: Prospective repeated measures study

Devices to be used: Only commercially available or off-the-shelf CE-marked devices are used: microphone systems, Actiwatch Spectrum, and polysomnography (PSG) recording devices.

Study population: 10 healthy adult nurses or doctors (in training) that are not currently working in the ICU.

Main study parameters/endpoints: Sleep-related parameters (arousals, sleep efficiency, sleep continuity, total sleep time) and the correlation of these with environmental parameters (light, sound, temperature).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no foreseeable risk involved with participation in this study. Because the participants will be medical professionals with work experience in the ICU the psychological burden will be negligible, compared to non-ICU experienced participants.

Participating parties and their roles: This single center study is sponsored by Philips Research, in cooperation with the ICU of the UMCG.

Study procedures: Before the start of the study subjects will be tested for normal hearing. Participants will first wear an Actiwatch for 7 days during a work week to gain insight into their normal sleep-wake pattern. Thereafter each participant will sleep one night at home, one night in a closed ICU section, and one night in an active ICU, all with PSG and sound and light recording. During the study participants will keep a sleep diary and fill out a short sleep questionnaire. Subjects will abstain from consuming alcohol all day and caffeine from 12:00 AM before each night of PSG recording. Monitoring will take place between the hours of 22:00 and 7:00. The study will not interfere with regular patient care.

1. INTRODUCTION AND RATIONALE

1.1 Introduction

1.1.1 Sleep neurobiology

Disrupted sleep in humans is associated with impaired immune function, increased susceptibility to infections (1–3) alterations in nitrogen balance, impaired wound healing (1,3) and impairment of neurophysiologic organization and consolidation of memory (2). In intensive care unit (ICU) patients this may consequently lead to the development of delirium, prolonged admission and increased mortality risk (2). Clearly, sleep is essential for human homeostasis, recovery and survival (4).

Sleep can be divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (2,5). Based on the criteria formulated by Rechtschaffen and Kales (R&K) [6] NREM sleep can further be divided into three stages (N1, N2 and N3) based on the presence of features such as specific frequency bands, sleep-spindles and K-complexes in the electroencephalogram (EEG). The stages N3, also known as slow-wave sleep (SWS), and REM are believed to be the most important for the restorative function of sleep (2). During sleep the different sleep stages occur in cycles of around 90 minutes each in healthy subjects (2,5).

However, most ICU patients have disturbed sleeping patterns, as is shown in numerous studies using polysomnography (the gold standard for evaluating sleep) (1,4,6,7). These sleep disturbances are characterized by severe fragmentation and frequent arousals and awakenings (6,8). An arousal is defined as a wake period of between 3-10 seconds, after which sleep resumes. One study described a median duration of sleep without waking of only 3 minutes (9). The sleep architecture is disturbed with more stage 1 and stage 2 NREM sleep present, while the critically important SWS and REM sleep stages are less prevalent (3,5,9). Further, it has been reported that ICU patients spend up to half of their total sleep time during the daytime (3,6,9,10). Finally, the traditional R&K sleep scoring criteria are often not uniformly applicable in critically ill patients because of the presence of atypical EEG activity (8,11).

1.1.2 The ICU environment and sleep

Patients admitted to an ICU are exposed to several intrinsic and extrinsic sleep disruptive factors. Intrinsic factors are mostly related to the critical illness itself and resulting

conditions, such as a disturbed circadian rhythm. This disturbance is thought to be important in the observed changes in distribution of sleep over the day. Extrinsic factors are environmental, such as uncomfortable temperature and high levels of noise and light during the night, and medical interventions. A multitude of these factors, most of them interrelated, is thought to play a role in the observed disruption of sleep in the ICU. However, the precise contribution of each factor remains unclear (2,5,12).

In all ICUs sound levels are much higher than recommended by the World Health Organisation (WHO) for hospitals, as is shown in many studies (13–18). However, the relative contribution of this environmental factor to sleep disturbance in ICU patients is difficult to assess. In patients, researchers have only been able to correlate 10-40% of arousals and awakenings to sudden peaks in sound (19,20). Additionally, patients in critical care settings have limited or nonexistent exposure to circadian rhythm stimuli such as bright light (21). Artificial lighting is of insufficient intensity and the timing of light exposure is often counterproductive because exposure at night, even at lower intensities, has an adverse effect on sleep timing (21). Further, studies examining the effectiveness of sleep promoting interventions show various results ranging between deterioration and relative improvements of 10% to 68% (22), using various approaches such as behaviour modification, earplugs, eye masks, sound masking by adding other sounds and improving absorption using acoustic materials. In one study sleep quantity and quality even seemed to be less after implementation of behaviour modifications (23). The causes of non-response to these interventions observed in some patients remains unclear (23,24).

Studying the primary effects of the busy ICU environment is complicated in patients. First of all, it will be unclear whether intrinsic or extrinsic factors are most important. Ventilator interactions, underlying illness, medications, nursing interventions, and the environment will all contribute to sleep disruption (25), making it extremely hard to determine the relative effect of each individual factor (18,22,26). To complicate matters even further a nursing intervention or for example patient/ventilator asynchrony may trigger an alarm, which may lead to arousals or awakenings to be registered as being caused by a sound peak when in fact it was caused by the event triggering the alarm (7). Secondly, EEG recordings in ICU patients are challenging to interpret because of altered EEG patterns, that hamper sleep staging in accordance with the R&K sleep scoring rules(2,26–28).

Studying the primary effects of the busy ICU environment can therefore best be done in a more homogenous and controllable group of healthy volunteers. A study by Stanchina et al.

(25) used a simulated ICU environment to study the isolated effects of recorded ICU sound on 5 healthy subjects. In this study 63% of the observed arousals could be related to peaks in sound. In other studies regarding sleep in healthy subjects in a simulated ICU environment, sound was often (partly) modified to study the effect of this modification (25,27), or the correlation between arousals and sound peaks was not investigated at all (29).

Although simulating the ICU environment is very suitable to study interventions in the sound environment, the results cannot plainly be extrapolated to a real ICU environment (28). The acoustic characteristics in ICUs are caused by complicated, multiple and dynamic noise sources (22). The playback of noise through speakers may lead to greater sleep disruption caused by magnification of the sound effect (25), as has been shown in this review (30), which found large differences in sleep disturbance between laboratory and field settings in other noisy environments. Further, sound and noise are very complex phenomenon and the meaning of the sound, among other factors, is also critical for the amount of disturbance (19,31). This suggests that recorded ICU noise might have a smaller effect on sleep disturbance because of the different subjective experience. Further disturbed sleep is often experienced in novel environments (32). This effect may be expected to be larger in a real ICU compared to a simulated environment.

Gabor et al. (20) placed 6 healthy subjects between critically ill patients in an active ICU. They could relate 69% of arousals and 58% of awakenings to peaks in sound when the subjects lay in an open ICU. In a single room, sound was deemed responsible for 47% and 37% of arousals and awakenings, respectively. This suggests that in healthy subjects noise is responsible for the majority of sleep disruptions.

1.1.3 Sound

When studying the effects of sound on quality, quantity and distribution of sleep not only the absolute sound level is relevant. Young, healthy volunteers are known to be able to raise their arousal threshold for noise to up to 80 dB(A) (decibels, adjusted for the range of normal hearing) (19,33). This was demonstrated by repeatedly waking the subject using an ascending series of 1000 Hz tones (33). In older subjects increasing the arousal threshold took more time and also a lower level of about 70 dB(A) was reached. The difference between measured peak and background sound levels is important because arousal thresholds can be increased by reducing the difference between background noise and peak noise (25). Also continuous stimuli (such as traffic noise) are less arousing than

intermittent stimuli (such as a ringing phone). Furthermore, other acoustic parameters such as sound spectrum and reverberation time are also important (22,34). The nature and origin of the sound influences the likelihood of a subsequent arousal (25,35). Arousals are much more likely to result from the sound of an alarm or a conversation than from traffic noise at the same sound level (35). It seems the more information present in a sound, the more difficult it becomes to ignore it.

1.1.4 Light, temperature and sleep location

The light-dark cycle is a so-called synchronizer or *zeitgeber* of the human sleep-wake cycle (18). Because in most humans the circadian cycle is slightly longer than 24 hours it must be realigned with the Earth's day-night cycle on a daily basis (21). The main factor that normally entrains the biological clock is presence and absence of short wavelength light (446-483 nm) during the day and the night respectively (36,37). Without this realignment a "free running" rhythm can develop (21). Patients in critical care settings often have very minimal exposure to environmental cues indicating day and night, such as bright light and behavioural functions including timing of meals.

The thermal environment is important in human sleep (38). Sleep time and sleep efficiency increase when sleeping in a room with a lower temperature (39). Some studies also reported a larger amount of REM and SWS (39).

Finally, also the sleep location and the familiarity with this location plays a role (40). It has been shown that subjects undergoing ambulatory PSG at home sleep longer and more efficient compared to when they undergo in-hospital PSG (41). This phenomenon is called the "first-night effect" and is most present during the first night in an unfamiliar environment (42). The most frequently reported characteristic of this effect is prolonged sleep latency. A recent study by Tamaki et al. (32) shows the first-night effect is caused by one hemisphere being more vigilant and acting as a night watch to monitor unfamiliar surroundings during sleep. A summary of the parameters affecting sleep is shown in figure 1.

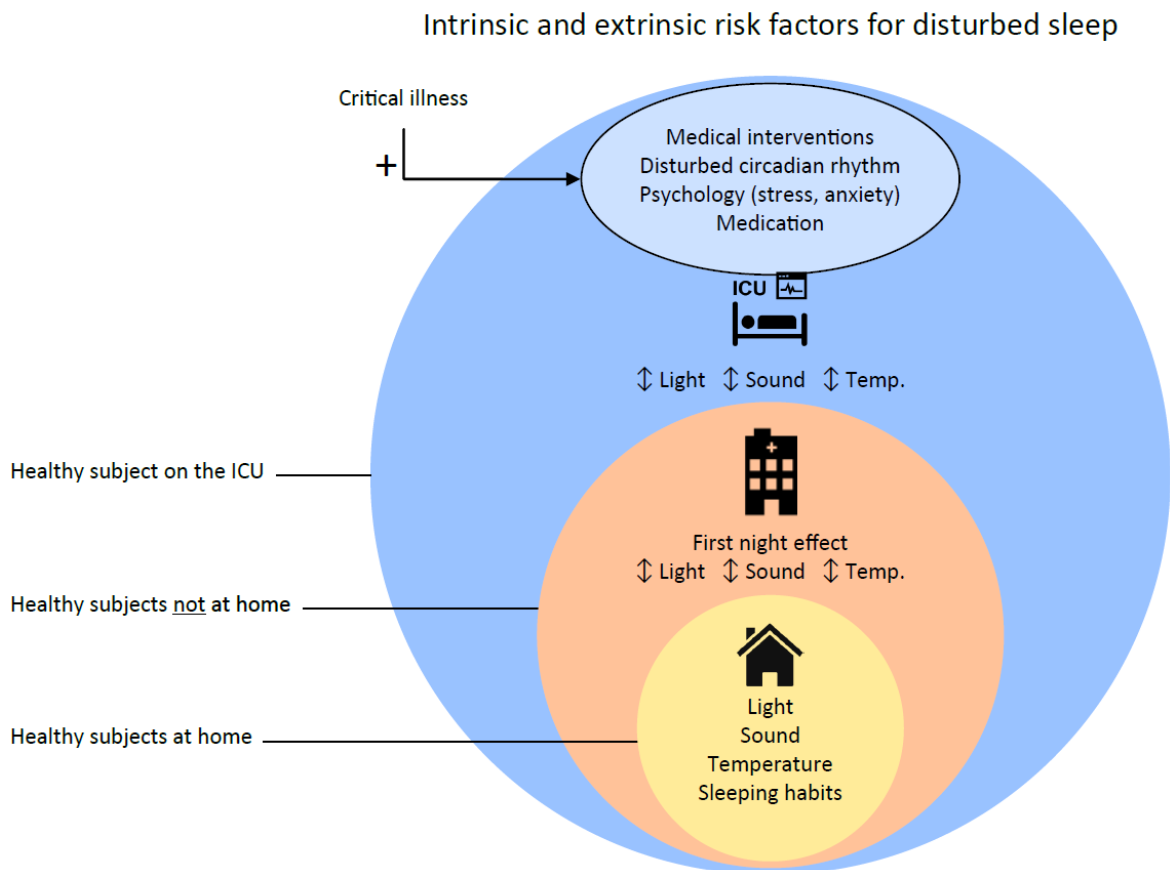


Figure 3: Overview of the risk factors for disturbed sleep organized by sleeping environment. By measuring in healthy volunteers we eliminate all parameters related to critical illness (striped oval). People are known to sleep best at home in a familiar environment with light, sound and temperature levels that they are accustomed to (yellow circle). When one is sleeping away from home, in for example a quiet hospital room, the first night effect and different light, sound and temperature levels will cause alterations to the sleeping pattern (orange circle). In the ICU environment the increased light and sound level and again a different temperature will effect sleep (blue circle).

1.2 Rationale

Studies examining the effectiveness of sleep promoting interventions show varying results but can be very cost-effective. However, it remains unclear why some patients do not respond to such interventions (23,24).

The first step in getting a better understanding of the relation between sleep and the ICU environment is to analyse the isolated effects of the sensory stress that accompanies admission to the ICU. By studying healthy subjects' sleep in an active ICU environment, the relative importance of the environment in the disturbance of sleep can be determined (figure 1). Several studies have attempted to simulate the experience of being admitted to an ICU, but none have been able to replicate the full multi-sensory experience (29). To our knowledge only one small study has ever investigated the influence of an actual ICU on healthy subjects' sleep. Therefore more data is

needed to get a better understanding about the effect of the ICU environment on people. Particularly the analysis of the noise present in the ICU should be done more thoroughly (22).

Primarily, this study will investigate the role of sound, light and the inherent experience of the ICU environment on the incidence of arousals, and therefore the continuity of sleep. Focusing on the study of healthy subjects eliminates confounding and immeasurable intrinsic factors present in patients that may interfere with clear analysis of this relation.

1.3 Objectives

1.3.1 Primary Objective:

- To investigate the correlation between stressors present in the ICU environment and continuity of sleep, in healthy subjects.

1.3.2 Secondary Objective:

- To determine the quality, quantity and distribution of sleep in healthy subjects in different environments.

1.3.3 Other objective:

- To use the gathered EEG data to help validate new sleep scoring algorithms.

2. STUDY DESIGN

During this prospective repeated measures study, healthy subjects will be exposed to different sleep environments including an operational ICU. It is designed to examine two main areas of interest (Table 1): quality of sleep and the sensory environment of the ICU patient. The environmental factors that will be measured are sound, light and temperature.

Table1: These two pillars will be monitored throughout the study.

	Sleep/Activity		Environmental factors			
	PSG	Actigraphy	Sound (ICU)	Sound (home)	Light	Temperature
Tool	EEG	Actiwatch	Microphone	Smartphone	Actiwatch	Thermometer
Sample rate	256 Hz	1 Hz	48 kHz	1Hz	1 Hz	15 minutes
Primary outcome	Arousals/hr	Distribution of sleep and wake	Decibel levels	Decibel levels	Light intensity	Degrees Celsius
Secondary outcomes	Sleep quantity and quality	-	Reverb. time, spectral components	-	Short wavelength light	-
Facilitator	UMCG	Philips Research	Philips Research	Philips research	Philips Research	UMCG

Subjects will be monitored during 3 study nights: home, closed ICU and active ICU, see figure 1. The subjects will be randomly assigned to one of two groups that undergo the ICU study nights in a different order. This helps to discriminate between the effects of a noisy environment and sleeping in unfamiliar surroundings. A flow chart is presented in Figure 2. First the subject will keep a sleep diary for 7 days to gain insight into the subject's sleep-wake pattern. Then one night will be spent at home with PSG as a baseline measurement for the subject's sleep architecture (home night). One night will be spent in a closed section of the ICU (separate, unused room (usually used for care of patients requiring isolation)) to measure the effect of sleeping in an unfamiliar environment and as a baseline for the sound and light measurement (control night). Finally, one night will be spent in an active ICU (ICU night). A location on the available ICUs exposed to a representative amount of ICU sound will be selected. The control and ICU nights will be done in the same unit. Due to structural overcapacity,

assigning a bed for the purpose of this study will not interfere with normal workflow. In the unlikely case that a conflict does arise patientcare will always prevail and the study will be suspended for the remainder of the night in question. To prevent acclimatization there will be a minimum three day interval between the separate study nights. Subjects will keep a sleep diary and fill in some short sleep questionnaires on the day of the measurements.

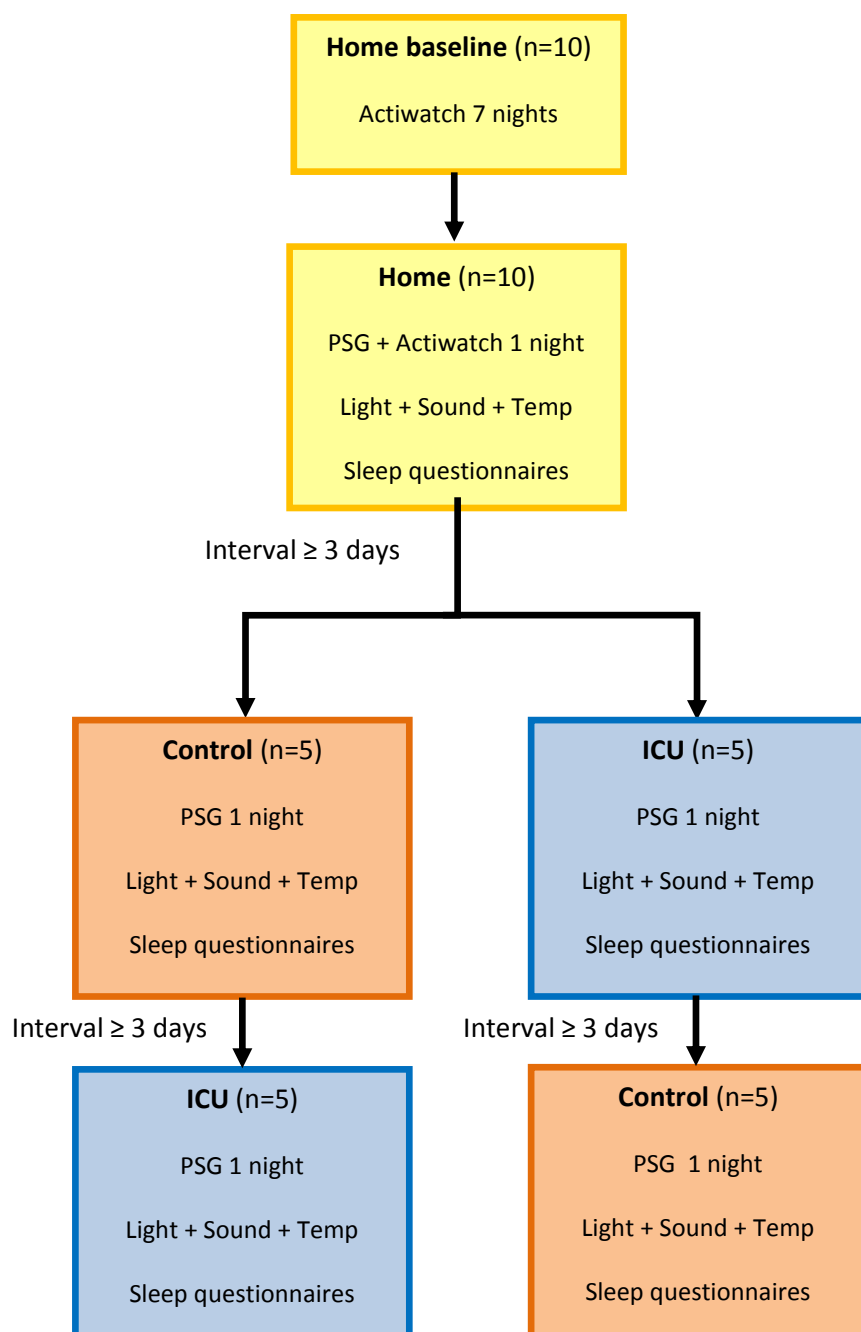


Figure 2: Flow chart with the chronological order and required equipment of each study night.

3. STUDY POPULATION

3.1 Population (base)

Studying the primary effects of the busy ICU environment is complicated in patients because it is almost impossible to determine the relative contribution of individual intrinsic and extrinsic factors in disturbing sleep. Secondly, EEG recordings in ICU patients are more challenging to interpret because they often do not meet R&K sleep scoring criteria. Therefore the primary effects of the busy ICU environment can best be studied in healthy volunteers.

These volunteers will be medical professionals. Nurses and doctors (in training) are familiar with the hospital environment, patients, and hospital regulations. Therefore the physiological burden will be negligible. By selecting only volunteers that are working in other departments they will however be unfamiliar with the characteristic sights and sounds present in the ICU.

3.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Healthy volunteers (nurses/doctors (in training)) that are not currently working in the ICU
- Age ≥ 18 years
- Capable of understanding and speaking Dutch
- Normal hearing

3.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Pre-existing history or treatment of sleep pathology
 - Sleep promoting medication (such as benzodiazepines)
- Alcohol addiction or illicit drug abuse

3.4 Sample size calculation

Sample size calculations were performed for the study parameter “number of arousals per hour” using the G*Power 3.1 (University of Kiel, Germany (43)) application. The effect size is based on the difference between baseline and ICU noise measurements from scientific literature.

To detect a significant change in the “number of arousals per hour” an a priori two tailed independent t-test was assumed based on data ($n=40$) from Huang et al. (28). The correlation between the baseline and noise measurements was not known. With $\alpha=0.05$ and $\beta=0.8$ this

results in an estimated required sample size of 10 subjects. Because our study design uses repeated measures the true required sample size is expected to be smaller, however, to compensate for possible loss of data 10 subjects will be included in the study.

4. METHODS

4.1 Primary study parameters

- Sleep-related parameters (using EEG: Rechtschaffen & Kales (R&K) manual scoring)
 - Number of arousals (and awakenings) per hour
 - Sleep efficiency (total sleep time/time in bed)
 - Sleep continuity (latency to sleep onset, number of awakenings after sleep onset, total time of wakefulness after sleep onset, time spent in sleep bouts (<10 min.), short naps (10 min.< 30 min.) and long naps (>30 min.))
 - Total sleep time (any sleep stage other than awake, derived from EEG)
- Correlation between sleep continuity and environmental parameters
 - Percentage of arousals caused by sound

4.2 Secondary study parameters

- Environmental parameters:
 - Sound levels (decibel and amplitude of spectral components)
 - Reverberation time
 - Light levels (Lux)
 - Light frequencies
 - Temperature (degrees Celsius)

4.3 Study procedures

Nurses and doctors (in training) that are currently employed in another department than the ICU will be actively recruited. Information about the study will be provided in writing, such as through posters, and also information meetings will be organised. Persons interested in the study will be screened for eligibility. The screening and consent procedure will be executed by the investigator. The potential volunteers do not have a dependent working relation with the investigator. The investigator will also make sure all data is stored only using the subject identification code. The study will require 10 subjects to be included. Before recruitment and enrolment in the study, each subject will be given a full explanation of the study and will be informed that he/she is free to discontinue the participation in the study at any time.

Before the start of the study, subjects will be tested for normal hearing. Sleep measurements will be performed using actigraphy and PSG. Subjects will start with keeping a sleep diary and wearing an Actiwatch for a duration of 7 days to gain insight into their sleep-wake pattern. Following this each participant will sleep one night at home with PSG and sound and light recording, one night in

a closed section of the ICU with PSG and sound and light recording and one night in the active ICU with PSG and sound recording. A schematic overview of the study procedures is shown in figure 3.

Subjects will receive instructions on hygiene, safety and behavior in the ICU. Subjects will also receive clear instructions on the rules of the study during their stay in the ICU. The staff will also be informed about these rules. Subjects will be physically isolated from patients. Island nursing is part of the normal workflow, subjects are not connected to any patient monitoring system and there will not be any subject-patient or subject-staff interaction. Also a subject's bed space will not neighbour a patient with a high risk of contamination ("isolatiedbed"). If any questions arise the investigator can immediately be contacted by phone. For medical questions during the study prof. dr. J.E. Tulleken, MD can be contacted. Subjects will abstain from consuming alcohol on the day before PSG measurements and abstain from caffeine consumption after 12:00 am on these days, because these substances are known to interfere with normal sleep (44,45). The half-life of caffeine is 3-7 hours (46). A moderate caffeine dose 6 hours prior to bedtime has been shown to have a significant effect on sleep (45). Even a small dose in the morning still gives a measureable effect on sleep, although not on subjective sleep experience (47). During the study participants will keep a sleep diary and will fill out the Richards-Campbell Sleep Questionnaire (RCSQ), Karolinska Sleepiness Scale (KSS) and the Samn-Perelli Fatigue Scale (SPFS) daily. PSG measurements will be scheduled at least 7 days after the last night-shift of the test person. Also the night following the measurement should not be a night-shift.

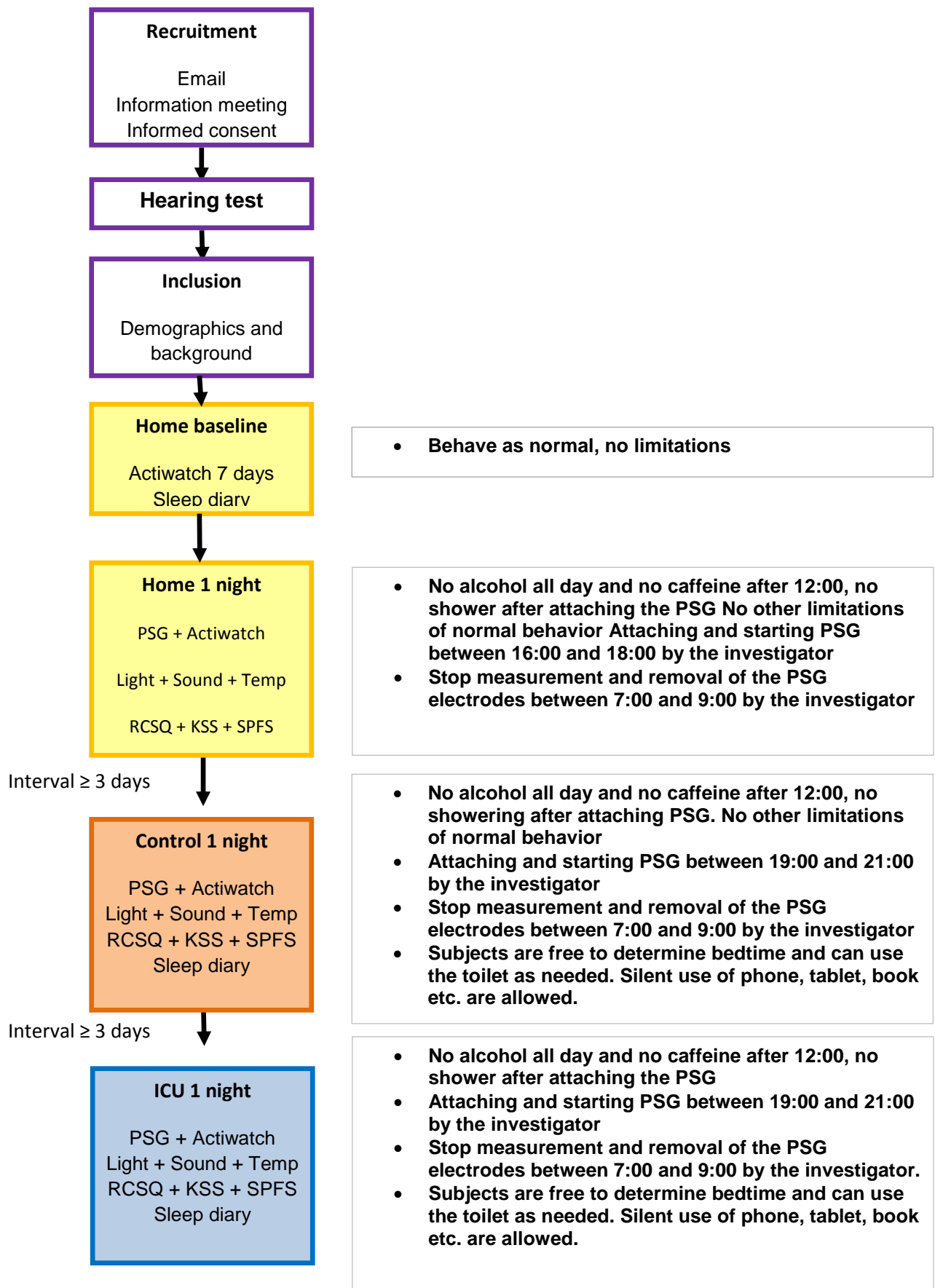


Figure 3: Schematic overview of study procedures

4.3.1 Demographics and background

The following demographic and background information will be recorded: age, gender, height, weight, profession, number of working hours per week, years of work experience, nightshifts per month, average number of successive nightshifts, smoking habits, caffeine and alcohol consumption habits and number and age of children living at home.

4.3.1 Hearing

Hearing abilities will be tested using the Dutch National Hearing Test, which is a validated (sensitivity: 0.91, specificity: 0.93) and easy to perform speech-in-noise test using digit-triplets as speech material (48). If this test indicates normal hearing the hearing threshold will be checked for tones of 0.125, 0.25, 0.5, 1, 2, 4, 8 kHz to confirm if there are no large differences in hearing capabilities for these specific frequencies between test persons (using sound files producing equal loudness contours, from School of Physics, University of New South Wales, Sydney, Australia). The tests will all be conducted in the same room using the same equipment.

4.3.2 Sleep

Subjects will fill in a sleep diary on bedtime, lights-out time, estimated sleep onset time, estimated wake after sleep onset, estimated wake time and rise time. Also part of the sleep diary is a question about caffeine consumption. During the baseline week at home sleep will also be measured using an Actiwatch. This is a commercially available device that can monitor activity, sleeping pattern and light exposure.

Subjects will wear the Actiwatch all day, except during working hours and when taking a shower. The Actiwatch data will be used to complement the sleep data in case a subject forgets an entry or cannot remember certain events.

During the Home, Control, and ICU nights, sleep quality, quantity and distribution will be measured using PSG. Sleep will be monitored during the night between the hours of 22:00 and 7:00. The electrodes necessary for PSG will be placed on the scalp of the subject using a special adhesive. According to the international 10-20 standard system these will be: F3, F4, A1/M1, A2/M2, C3, C4, O1, O2, ground and reference. Together with these EEG electrodes two electro oculography (EOG) electrodes will be placed on the left-top and right-bottom near the eye. Two electro myography (EMG) electrodes will be placed on the jaw muscles according to normal protocol. The electrodes will be attached by the investigator, which takes approximately one hour per subject per day. These records will be stored digitally for

evaluation. At the end of each study night the investigator removes the applied electrodes, which takes approximately 15 minutes. There are no known side effects regarding the adhesion of electrodes. Some skin irritation caused by the adhesive may occur. Thus far 27 patients have undergone PSG recordings in a related study in our centre without any problems. Only one patient complained about mild itching which subsided when the electrodes were removed.

An ambulatory PSG recorder (used for outpatient recordings) available from the department of clinical neurophysiology will be used. This device is designed and exclusively used to measure sleep in the home setting. It therefore does not interfere with daily activities and sleep comfort. Measurements will be scheduled in a way that they do not interfere with the normal workflow, and at a day and time that is convenient for the subject. For the hospital PSG recordings, a dedicated stationary EEG-device will be used.

4.3.3 Sleep Questionnaires

The Richards-Campbell Sleep Questionnaire is a validated 5-item VAS questionnaire (49). The questions concern sleep depth, sleep latency, awakenings, returning to sleep, and sleep quality. For this study a 6th item concerning noise will be added. Subjects will also fill out the Karolinska Sleepiness Scale, a subjective scale used to measure sleepiness on a scale ranging from 1 to 9, with 1=very alert; 3=alert; 5=neither alert nor sleepy; 7 sleepy, but no effort to keep awake; 9=very sleepy great effort to keep awake (50), and the Samn-Perelli Fatigue Scale, which provides a subjective measure of fatigue on a scale ranging from 1 to 7, with 1=fully alert; wide awake; 2=very lively, responsive, but not at peak; 3=okay, somewhat fresh; 4=a little tired, less than fresh; 5=moderately tired, let down; 6=extremely tired, very difficult to concentrate; 7=completely exhausted, unable to function effectively (51). All questionnaires are translated to Dutch.

4.4 Devices

For PSG measurements, locally available equipment will be used. All tools and devices specifically used for data collection in this study are either commercially available, or validated off-the-shelf devices. All measurement systems are CE-marked and exclusively configured and operated by the investigators or skilled personnel. The devices obtained specifically for this study are individually discussed in detail below.

4.4.1 Sound

For sound level monitoring in the hospital, a standard audio setup is constructed from off-the-shelf components. The sound captured by the microphone is input for a signal processing software that calculates sound pressure levels in real-time. Only the sound pressure levels are stored. There is no software running on the device to store the original sound scape captured by the microphone. The microphone is positioned close to, but above the subject's bed. It is attached to the large instrument-arches, present over all ICU beds, or to the ceiling in the private study room. Through a soundcard, the device is connected to HP research laptops, property of the UMCG. The selected microphone mentioned in the table below is capable of a flat frequency response up-to 23 kHz. Sampling rate of this device is kept at 48 kHz to fulfil the Nyquist-Shannon sampling theorem.

	Device	Make/model	Remark
1	Microphone	Earthworks M23	
2	Audio interface to PC	Steinberg CL1	USB sound card
3	Laptop computer	HP probook 6560b	
4	Laptop power supply	HP factory standard	

For sound level monitoring at home a smartphone with an application for sound measurement is used instead. This app is designed for monitoring the non-medical environment of the ICU and stores sound level data (dB) at a one second interval. To maintain comparability of sound measurements, the smartphone will also be used in the hospital settings.

4.4.2 Light

For illuminance and irradiance measurements, a commercially available Actiwatch Spectrum will be used. The device stores illuminance between 400-700nm and irradiance for three separate 100nm bands on local memory. The normally wrist worn device will be placed on the bedhead, which monitors light intensity of 3 major spectral bands (red, green and blue) during the study period.

4.4.3 EEG

The UMCG has several commercially available CE marked EEG devices at its disposal for routine EEG and PSG measurements. These devices will be used for the purposes of this study depending on their availability. Only experienced, trained technicians and the investigators will install and remove the electrodes connected to these devices.

4.4.4 Temperature

For temperature measurements a digital environmental USB-temperature logger will be used.

4.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences or explanation.

4.6 Replacement of individual subjects after withdrawal

Individual subjects will be replaced after withdrawal.

4.7 Follow-up of subjects withdrawn from treatment

There will be no follow up of subjects withdrawn from observation.

4.8 Premature termination of the study

At this time there are no foreseeable reasons, why the study should be stopped prematurely. Theoretically, practical objections to the proposed method could cause premature termination of the currently formulated study and will result in formulation of a revised protocol. The data collected up to the point of terminating the study will be kept available for research purposes.

5. SAFETY REPORTING

5.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

5.2 AEs and SAEs

5.2.1 Adverse events (AEs) and adverse device effects (ADEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study. Potentially, these are related to diagnostic procedures or pre-existing conditions. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. The investigator shall report serious adverse events to the Study Manager of the sponsor without undue delay after obtaining knowledge of the events. Adverse device effects shall be reported to the Q&R office of the sponsor as well. The Director Q&R shall assess the ADEs for reportability to Competent Authorities.

5.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

All adverse events shall be reported to the Study Manager. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events. SAEs shall be reported to the Q&R office of the sponsor as well. The Director Q&R shall assess the SAEs for reportability to Competent Authorities.

5.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

6. STATISTICAL ANALYSIS

The EEG data will be assessed using the gold standard of manual scoring by a neurologist. Additionally, it will also be used to help validate new scoring algorithms. The collected data will be statistically analysed with the use of SPSS 21. All other signal processing and analyses will be performed using Matlab 2014b, with various toolboxes for EEG data-analysis, curve fitting and visualization of results. Normality of the distribution of samples will be tested using the Kolmogorov-Smirnov test. In case of normal distribution, two-tailed T-tests are used to potentially compare means between groups, such as between different study environments and age-groups (40 years and older versus younger than 40 years of age). In case of non-normal distribution, Mann-Whitney U-tests will be used to compare means.

The estimation of the correlation between sleep and environmental parameters is combined with descriptive statistics, to determine which environmental factors are associated with disturbed sleep. To examine the association of quality of sleep parameters with environmental parameters, we will use repeated measures ANOVA. Other descriptive statistics (such as age, BMI, etc.) are considered as covariates.

6.1 Primary study parameters

Statistical analysis of the quality and quantity of sleep consists of the PSG-parameters: total sleep time (TST), sleep efficiency, percentage of TST spent in REM sleep, percentage of TST spent in stage 1, stage 2, and slow-wave sleep (SWS, NREM stages 3 & 4), and the number of arousals and awakenings. These parameters determine quantitatively and qualitatively the degree in which sleep is affected in healthy subjects in the ICU. An arousal will be scored as a response to a sound stimulus if it lasts more than three seconds during or up to 15 seconds after a sound stimulus (34). From this the percentage of arousals caused by sound will be calculated.

6.2 Secondary study parameters

Illuminance, irradiance, temperature and the amount and spectrum of sound are measured at the bedside. These continuous data are used to characterize the environment and to determine the association between these environmental factors and sleep.

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

All participants will be informed of the aims of the study. They will be informed as to the strict confidentiality of their participant data. It will be emphasized that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he/she wants. Documented informed consent must be obtained for all participants included in the study before they are registered in the study. This study is conducted in agreement with the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

7.2 Recruitment and consent

Persons interested in participating in the study will be screened and asked for consent. The screening includes verifying that the participant does not have a pre-existing history or treatment of sleep pathology, does not have a history of alcohol or drug abuse (both by asking the participant) and a hearing screening test (detailed information in paragraph 4.3.2). Participants will be informed on the study by an investigator. The investigator will give the participant the information needed for an informed decision. The exact time of being informed, and the time of consent will be logged and stored. Upon consent of the participant the informed consent form will be signed by the participant and the investigator. The participant information letter and informed consent form are attached as a separate document.

7.3 Benefits and risks assessment, group relatedness

There is no foreseeable risk involved with participation in this study. All tools and devices used for data collection are CE-marked and either commercially available, or validated off-the-shelf devices. Sound and light monitoring will be restricted to the spectrum and sound/light level, to minimize the risk of privacy violation. There is no direct benefit for participants.

7.4 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO. Participation in this study involves no risks for the subject. Therefore, the Medical Ethical Committee of the UMCG has concluded that no insurance, other than the liability insurance, is required for this study.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.1 Handling and storage of data and documents

All data will be dealt with confidentially and anonymously. A subject identification code list will be used to keep the data from each subject together. The code will not be based on any relatable subject characteristics. The code will consist of a serial number according to time of entering the study. The key to the code will be safeguarded by the principal investigator and will only be used in case the subject decides to withdraw from the study. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: de Wet Bescherming Persoonsgegevens, WBP).

Only anonymized digital data will be shared with Philips by the institution. These digital data are stored on an encrypted Philips laptop for transportation. Philips will store these data until no longer useful. The usefulness of the data is reviewed periodically, every 5 years.

8.2 Monitoring

A monitor supplied by the sponsor, not affiliated with the ICU, will monitor the study. The monitor will ensure that:

- All involved caregivers (e.g. nurses) are properly instructed and informed about the study: an instruction manual and a quick reference card will be available.
- The consent process is executed adequately
- The study is executed according to the study protocol
- The devices are installed according to the protocol and risk management plan
- The data are anonymized (coded) before submitting them to Philips or other parties
- (Serious) Adverse Events are handled according to the protocol

8.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All amendments that require METC approval (according to the ISO 14155) will be submitted to the METC for approval.

8.4 Annual progress report

The duration of inclusion of subjects is expected to be completed within a few months. Therefore no annual progress report will be submitted to the accredited METC.

8.5 End of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks after conclusion of the study. The end of the study is defined as the last subject's last visit. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

8.6 Public disclosure and publication policy

Research data will be stored, analysed and eligible for publication. Only the UMCG will have access to the anonymized data for their research purposes. Results that are extracted from the data can be published in scientific journals after protecting IP. The study will be prospectively registered in a public trial database. The decision to publish will be made independent of the outcome of this study. If published, the research data will be publicly disclosed and published independent of the outcome of this study. Members of the writing committee including the (principal) investigator(s) will all participate in the publication process.

The (Principal) Investigators must submit to Philips any abstract, manuscript, or other communication relating for review 60 days prior to submission for publication. Publications are only allowed after the Clinical Investigation has been completed. Philips retains the right to review and revise the manuscript to ensure protection of proprietary or other confidential commercial information and compliance with regulatory requirements.

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