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Auditory frequency processing during wakefulness and sleep

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RÉSUMÉ

Apprendre une nouvelle langue ou de nouvelles compétences pendant le sommeil serait un rêve devenu réalité pour plusieurs. Pendant des décennies, cette idée a été rejetée en se basant sur la supposition que le cerveau endormi ne répond pas et est plutôt isolé. Par contre, quelques études démontrent que de l'information auditive pourrait être perçue et traitée pendant le sommeil, et que même de la nouvelle information pourrait être acquise. Toutefois, très peu est connu au sujet du type d'information qui peut être traitée, et si les étapes de traitement durant le sommeil sont comparables à celles effectuées pendant l'éveil. Le but de cette thèse est d'investiguer le traitement de fréquences auditives pendant le sommeil relativement à l'éveil. Tout au long de cette thèse, l'adaptation est utilisée pour vérifier le traitement fréquentiel (i.e., l'adaptation réfère à une réduction en activation corticale pour un signal prolongé ou répété). Nous avons testé la possibilité de modifier le traitement fréquentiel cortical par l'écoute de musique filtrée pendant l'éveil, ainsi que l'exposition à du bruit filtré pendant une nuit complète de sommeil. Le filtre utilisé est un filtre coupe-bande qui enlève certaines fréquences du signal. De plus, le traitement d'information fréquentielle a été testé pendant une nuit complète de sommeil. Les résultats montrent que l'écoute de musique filtrée pendant plusieurs jours induit des changements au traitement fréquentiel cortical par rapport au filtre appliqué. Des changements similaires ont été détectés après une nuit d'exposition au bruit filtré, ce qui indique un haut niveau de perception et de traitement d'information du cerveau endormi. Par contre, aucune différence en réponse fréquentielle spécifique n'a pu être détectée pendant le sommeil, ce qui indique que l'adaptation pourrait fonctionner différemment pendant le sommeil et l'éveil.

Mots-clés: *Sommeil, traitement auditif, traitement fréquentiel, adaptation, filtre coupe-bande.*

ABSTRACT

Learning a new language or a new skill while sleeping would be the dream come true. For decades this idea has been rejected based on the assumption that the sleeping brain is rather unresponsive and isolated. However, a small number of studies demonstrate that auditory information could be perceived and processed during sleep, and that even new information could be acquired. It is still unknown which kind of information can be processed, and whether processing steps performed during sleep are comparable to those performed during wakefulness. The aim of this thesis is to investigate the processing of auditory frequency information during sleep relative to wakefulness. Throughout this thesis frequency processing was measured via adaptation. Adaptation refers to a reduction in cortical activation for a prolonged or repeatedly presented signal. We tested the possibility to alter cortical frequency processing via notched music listening during wakefulness, as well as via notched noise exposure during whole night sleep (i.e., notched-music and notched-noise are sound signals from which certain frequencies have been removed). Furthermore the processing of frequency information was tested throughout whole night sleep. Results show that several day long notched-music listening induces changes in cortical frequency processing relative to the applied notch. Similar changes were detected after one night of notched-noise exposure, indicating a higher level of auditory information processing of the sleeping brain. However no differences in frequency processing could be detected during sleep, indicating that adaptation might function differently during sleep relative to wakefulness.

Keywords: *Sleep, Auditory processing, Frequency processing, Adaptation, Notch.*

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AD	Adaptation test; Performed in notched-music listening study (Chapitre 2)
AM	Amplitude modulation test; Performed in notched-music listening study (Chapitre 2)
dB HL	Decibel Hearing Level
dB SPL	Decibel Sound Pressure Level
EEG	Electroencephalography, Neuroimaging technique
ERP	Event related potential
fMRI	Functional Magnetic Resonance Imaging, Neuroimaging technique
Hz	Hertz; Unit for frequency
MEG	Magnetoencephalography; Neuroimaging technique
REM	Rapid eye movement sleep
NREM	Non-rapid eye movement sleep
NREM-1	Non-rapid eye movement sleep – Sleep stage 1
NREM-2	Non-rapid eye movement sleep – Sleep stage 2
NREM-3	Non-rapid eye movement sleep – Sleep stage 3
N1	ERP component, Negative deflection of ERP waveform, around 100 ms after event onset
P2	ERP component; Positive deflection of ERP waveform, around 200 ms after event onset

CHAPITRE 1:

INTRODUCTION

1.1. Sleep

"*Sleep is the intermediate state between wakefulness and death; wakefulness being regarded as the active state of all the animal and intellectual functions, and death as that of their total suspension.*"

(Macnish, 1834; in Pelayo & Dement, 2017).

As indicated in this early definition, sleep has been considered a passive state in the beginning of sleep research. No clear differentiation was made between sleep and other states of low or no consciousness, like for example, coma or hibernation (Pelayo & Dement, 2017). Although the number of studies investigating sleep has increased tremendously over the last years, still little is known about its function and mechanisms (Walker & Stickgold, 2006). It is evident that, within a day, the human brain cycles through different levels of activity and arousal ranging from wakefulness to sleep. Sleep itself can be divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep. Within one night NREM sleep and REM sleep interchange within sleep cycles. The length of sleep cycles, the average sleeping time, as well as the NREM-REM sleep ratio change throughout lifetime. For a healthy young adult a normal sleep night consists of about 75% - 80% NREM sleep and 20% - 25% REM sleep. Short periods of wakefulness may also occur during an average night sleep.

Normal sleep begins with a NREM sleep period and the first REM sleep period might occur as early as 80 minutes after sleep onset. Thereafter NREM and REM sleep periods alternate in cycles of about 90 minutes, however REM sleep periods tend to become longer throughout the night (Carskadon & Dement, 2017).

Theories about dreaming and sleep can be dated back to the earth's earliest civilizations (Barbera, 2008). First research on sleep is tightly linked to the development of the Electroencephalography (EEG) method by Hans Berger in 1929 to measure electrical brain activity in humans. The EEG method allowed, for the first time, to perform sleep measurements with little or no disturbance for the sleeper (for a detailed historical review on sleep research see Dement, 1998). Today's sleep research requires, at least, the application of EEG, electromyography (EMG), and electrooculography (EOG), which, in combination, are essential to estimate the sleep onset and to identify sleep stages and sleep cycles (for an overview on sleep staging see Hirshkowitz, 2017; see also Keenan & Hirshkowitz, 2017). Polysomnography, which implies measures like, for example, leg movements, the airflow during respiration, or electrocardiography (ECG), can be applied additionally to test for indications of sleep disorders or abnormalities (Mendelson, 1987). The identification of sleep stages is based on predefined norms. The first standardized classification system for human sleep was developed by Rechtschaffen and Kales in 1968. Their system defined seven separate sleep stages and was applied for decades worldwide. In 2007 the American Academy of Sleep Medicine (AASM) introduced, not without controversy, a new guideline for sleep research (Carskadon & Dement, 2017). Following the 2007 guideline NREM sleep is divided into three stages, stage 1 (NREM-1), the onset period of sleep which is often also referred to as 'drowsiness', stage 2 (NREM-2), and stage 3 (NREM-3), which is also known to as slow wave

sleep (SWS) due to the dominance of delta activity, that is slow oscillating high amplitude waves, during this sleep stage (Carskadon & Dement, 2017). The EEG signal during REM sleep, or paradoxical sleep, seems rather desynchronized and the rapid low amplitude waves resemble brain activity during wakefulness (Maquet, 2001). REM sleep is usually treated as one uniform sleep stage, however it can be divided into tonic and phasic REM sleep (pREM and tREM) based on the presence or absence of rapid eye movements (Ferri & Fulda, 2017). The sleep research presented in this thesis is based on the 2007 guideline.

1.2. Sleep and Auditory processing

For decades is has been assumed that the sleeping brain is shut down and disconnected from its environment, an idea that was probably encouraged by the observable unresponsiveness to environmental events during sleep. Theories about the brain's functional disconnectivity have been proposed by a number of researchers (e.g, Horne, 1989; Pompeiano, 1970; Steriade, 1994; see also Hobson, 2005). However, everyday life experiences indicate that the sleeping brain can be reached. The simple fact that a loud sound, the nagging of an alarm clock, an increasing amount of light, or sensations of touch or movement can interrupt and terminate sleep, are clear evidence that sensory information can be received in the state of sleeping. However, as not every event leads to awakening, the interesting question is which events do and why? It has been suggested that auditory thresholds during sleep are elevated. Awakening thresholds have been reported to be near 70 - 90 db SPL (Bonnet, Johnson & Webb, 1978; Bonnet, 1982) which resembles a loudness ranging from a normal conversation to standing next to a busy street (Moore, 2008a). Beside the sound level, the significance of

the presented sound seem to play an important role. Oswald, Taylor, and Treisman (1960) showed that participants are more likely to awaken to their own name relative to any other name. A finding that has been replicated by a number of studies (e.g., Langford, Meddis & Pearson, 1974; McDonald, Schicht, Frazier, Shallenberger & Edwards, 1975; Voss & Harsh, 1998). Furthermore it has been shown that mothers awaken more easily by the sound of their baby (Formby, 1967; Poitras, Thorkildsen, Gagnon & Naiman, 1973).

Single-unit recordings (i.e., measure of single neuron responses) indicate that visual and somatosensory information can be processed during sleep, however cortical activations are more attenuated during sleep than during wakefulness (e.g., Evarts, 1963; Gücer, 1979; Livingstone & Hubel, 1981). Interestingly, results on auditory processing during sleep are more complex. While some studies suggest a decreased neural activity during sleep (e.g., Brugge & Merzenich, 1973; Czisch et al., 2004), others report similar activations during sleep and wakefulness (Portas et al., 2000), or even an elevated activity during sleep for a number of neurons (Peña, Pérez-Perera, Bouvier & Velluti, 1999; Edeline, Dutrieux, Manunta & Hennevin, 2001). Thalamic gating (McCormick & Bal, 1994; Steriade, McCormick & Sejnowski, 1993) has been considered to be the reason for the decreased neural activity found in the primary visual and somatosensory cortex during sleep. The less uniform results found in the auditory domain indicate that thalamic gating alone might not be a sufficient model to estimate or describe the effects of sleep on auditory processing (Issa & Wang, 2008).

1.3. Auditory frequency processing

An auditory signal carries a number of sound features like sound level, direction, and of course frequency. The frequency range of the human ear spans from about 16 Hz to 20 kHz

(Blauert, 1997), and is most sensitive for frequencies between 1 kHz and 4 kHz (Gazzaniga, Ivry & Mangun, 2009). The frequency information of a sound is processed in different levels along the auditory pathway. After a sound enters the ear channel, it is compressed and passed on to the cochlea which acts as a rough Fourier analyzer, transforming the sound information into frequency based activations (Moore, 2008a). The basilar membrane, located within the cochlea, is organized in a tonotopic fashion, that is each membrane segment responds to specific frequencies. Arriving sound information sets the basilar membrane into motion evoking peaks and valleys which resemble the sound's frequency composition. The movements, or better vibrations, of the basilar membrane are translated into afferent action potentials which are passed on from the auditory nerve through a number of subcortical structures to the primary and secondary auditory cortex. Throughout the auditory pathway neurons are thought to have frequency tuning and to remain organized based on frequencies in a tonotopic fashion (Gazzaniga, Ivry & Mangun, 2009; Romani, 1986; Bitterman, Mukamel, Malach, Fried & Nelken, 2008). Frequency tuning refers to an increased sensitivity for a specific frequency. The frequency that evokes the strongest neural response is called the 'best frequency' or 'critical frequency' (Moore, 2008a).

The processing of frequency information is rather flexible and can be altered due to active training or passive sound exposure. The intensive and persevering practice of musicians, for example, plays a substantial role in the superior frequency detection and discrimination accuracy found for musicians relative to non-musicians (e.g., Kishon-Rabin, Amir, Vexler & Zaltz, 2001; Lee, Skoe, Kraus & Ashley, 2009; Pantev et al., 1998). It has also been shown that the ability to discriminate frequencies can be improved in non-musicians within several days of training (e.g., Menning, Roberts & Pantev, 2000; Jäncke, Gaab,

Wüstenberg, Scheich & Heinze, 2001). Furthermore it has been demonstrated that cortical processing of frequency information can be altered when listening to notched music, that is music from which a frequency band has been removed. Listening to notched music for several days or months are reported to reduce the cortical processing of the removed frequencies (e.g., Okamoto, Stracke, Stoll & Pantev, 2010; Pantev, Wollbrink, Roberts, Engelien & Lütkenhöner, 1999). While all these findings indicate plasticity in the domain of auditory frequency processing, they are limited to the state of wakefulness. In fact still little is known about the general effect of sleep on the processing of auditory frequency information, and even less about the specific possibility to alter frequency processing in the sleeping brain. The research presented in this thesis has been performed to gain insights in exactly this area. Before presenting the performed studies and their outcomes in more detail, a short overview will be given about the applied research method and the specific research background.

1.4. Research method: EEG

1.4.1. General Information

EEG has been used as research method in all three studies described in this thesis. It is one of several functional neuroimaging techniques that have been developed in the last decades, and is widely used in research and day-to-day medical care. Comparing EEG to other, more recently developed functional neuroimaging techniques, it becomes evident that each of them has their own advantages and disadvantages. In comparison to functional magnetic resonance imaging (fMRI), for example, EEG has a higher temporal but a lower spatial resolution, which makes EEG preferable for time sensitive measurements.

Magnetoencephalography (MEG) is like EEG based on synaptic activity. However both methods differ in their sensitivity towards activation sources. While MEG captures mainly activations that create a dipole parallel towards the scalp (i.e., tangential sources), EEG captures activations with a dipole directed vertically towards the scalp (i.e., radial sources) as well as tangential sources. Related to the cortex, gyri are mostly radial sources, while sulci are mostly tangential sources (Srinivasan, 1999). The sensitivity differences between EEG and MEG implies that MEG can have a higher location accuracy, but might fail to detect the complete activation (Cohen et al., 1990; Shahin, Roberts, Miller, McDonald & Alain, 2007). Furthermore, the EEG method holds a higher level of flexibility. EEG electrodes are attached to the participants skull, and allow for a certain degree of head and body movements. The development of portable EEG systems allows even to move testings outside the laboratory setting. A number of sleep studies have been performed using fMRI or MEG (e.g., Portas et al., 2000; Manshanden, De Munck, Simon & da Silva, 2002; Horovitz et al., 2008; Klinzing, et al., 2016). However, as mentioned above, sleep research is historically tightly connected to EEG, and is still the method of choice especially when measuring whole night sleep. No other method has that little impact on normal sleep behaviour. Recordings can be performed with participants sleeping in a bed. The attached electrodes limit movements to some extent, however they still allow for average motions of head and body.

1.4.2. Event related potentials (ERPs)

EEG captures changes in cortical activation, which is based on synaptic activity of a large number of neurons (Light et al., 2010, Teplan, 2002). Small voltage changes are captured through electrodes which are attached to the subject’s scalp. To probe the response for

a specific stimulus, a large number stimulus repetitions is necessary to separate the stimulus related signal from the ongoing EEG signal. The required number of repetitions is based on the signal-to-noise ratio of the area of interest. Stimulus responses at the brainstem, for example, are rather small compared to the general brainstem activity, which calls for a high repetition rate per stimulus when performing recordings in this area (Colrain & Campbell, 2007; Teplan, 2002). The stimulus response averaged across repetitions is known as event related potential (ERP). ERPs are time-logged to the stimulus presentation. The level of cortical information processing is indicated by ERP components, which are positive and negative deflections of the ERP waveform (Näätänen & Winkler, 1999). ERP deflections that occur shortly after the stimulus onset (1 ms - 50 ms) are considered *sensory* or *exogenous* ERP components. They reflect activations at the beginning of the sensory pathway (peripheral and subcortical), and are highly dependent on physical features of the stimulus like, for example, its signal strength or its sensory modality. Later ERP deflections are considered *cognitive* or *endogenous* ERP components. They reflect cortical activations based on cognitive processes involved in the stimulus processing like, for example, attention or memory. Cognitive ERP components are complex and thought to originate from different generators (Bastuji & García-Larrea, 1999, Donchin, Ritter & McCallum, 1978; Näätänen & Winkler, 1999). ERP components can be divided further based on their latency, which is closely linked to the information processing along the auditory pathway. Early latencies, which occur within the first 10 ms after stimulus onset, indicate activations in the auditory nerve and brainstem, middle late latencies, around 10 ms to 50 ms after stimulus onset, indicate activity in the primary and secondary auditory cortex, and late latencies, which comprise a time range starting at 50 ms after stimulus onset, have cortical origin, reflect cognitive processing, and are

thought to be affected by vigilance, attention and experimental environment (Campbell & Colrain, 2002; Pratt, 2012).

The late auditory ERP components N1 and P2 are most relevant for the current thesis. When analyzed together, these two components are often referred to as 'vertex potential' (Crowley & Colrain, 2004). The N1 component is a negative deflection that occurs around 100 ms after stimulus onset. Its multiple generators are not fully understood, however they are thought to be located, bilaterally, in the supratemporal auditory cortex and in frontal regions (Atienza, Cantero & Escera, 2001a; Ibáñez, Martín, Hurtado & López, 2009). The P2 component is less well studied. Often it is only considered as part of the vertex potential, reduced to one peak-to-peak measure with the linked N1, and rarely treated as a functional independent component (Crowley & Colrain, 2004). The P2 is a positive deflection which occurs around 200 ms after stimulus onset and generates from multiple sources in frontal regions (Crowley & Colrain, 2004; Ibáñez et al., 2009). Both ERPs, N1 and P2, can be elicited by attended and unattended stimuli, which leads to the assumption that both components are partly exogenous responses (Crowley & Colrain, 2004). Functionally the N1 is thought to be evoked by transient changes in an auditory signal, and to reflect processing of physical stimuli features like intensity or location (see Näätänen & Picton, 1987). Similar to the N1, the P2 reflects processing of physical parameters like pitch or intensity. Furthermore the P2 is thought to be involved in the organization of stimulus information (see Crowley & Colrain, 2004).

1.4.3. ERPs and Sleep

ERPs can be measured passively, that is without active response behaviour of the participant, which makes them a great tool for sleep research (e.g., Cote, 2002; Ibáñez et al.,

2009). Although brain activity differs tremendously between states of wakefulness, REM sleep and NREM sleep (Hobson, 2005), most ERPs that can be measured during wakefulness also occur during sleep. While early latency ERPs are nearly unaffected by sleep, later ERP components tend to be state dependent (Atienza, Cantero & Escera, 2001a), that is features like latency and amplitude differ between wakefulness and sleep, as well as between the different sleep stages (e.g., Bastuji & García-Larrea, 1999; Colrain & Campbell, 2007; Ibáñez et al., 2009). The relation between potentials measured during wakefulness and sleep are still not fully understood and have to be treated with caution. For example, the P3, a late positive potential which is often related to the processing of attended stimuli and consciousness during wakefulness, has been reported by a number of authors to also occur during sleep (for a review see Cote 2002). While there is some evidence that a P3-like wave can be elicited during REM sleep (e.g., Niiyama et al., 1994; Bastuji et al., 1995), it is still highly debated to which extent this sleep-potential is related to a measure of attention and conscious. Concerning the N1 and P2, the ERP components relevant for the presented research, it has been shown that both components can be elicited during NREM and REM sleep. As mentioned above, the N1 component is studied more extensively than the P2 component, which holds true for research on sleep. It has been demonstrated that the N1 latency increases throughout NREM sleep, and adjusts slightly to the latency during wakefulness in REM sleep (Campbell & Colrain, 2002). The N1 amplitude decreases throughout NREM sleep, beginning with the sleep onset period (Bastuji, García-Larrea, Franc, & Mauguière, 1995; Nordby, Hugdahl, Stickgold, Bronnick & Hobson, 1996) and diminishes further during NREM-2 and NREM-3 (Van Hooff, De Beer, Brunia, Cluitmans & Korsten, 1997; Winter, Kok, Kenernans & Elton, 1995). During REM sleep the N1 amplitude recovers and augments to approximately a quarter or half of its awake

amplitude (Bastuji et al., 1995). Results for the less well studied P2 indicate, that the P2 amplitude increases throughout NREM sleep, from sleep onset period (Ogilvie, Simons, Kuderian, MacDonald & Rustenburg, 1991), to NREM-3 (Campbell, Bell & Bastien, 1992; Winter et al., 1995), and returns to about half their waking state amplitude during REM sleep (Crowley & Colrain, 2004). Considering the effects for both components, sleep seems to shift their activations towards a more positive response. Explanations for this sleep-related shift vary. Campbell, Bell and Bastien (1992) suggest that the differences are based on 'waking processing negativity', that is, attention induces a slow negative wave which alters N1 and P2 measures during wakefulness, and the non-existence of this negative wave during sleep results in the detected differences. Näätänen and Picton (1987) on the other hand suggest that sleep introduces a slow positive wave (for a discussion see Crowley & Colrain, 2004; see also Campbell & Colrain, 2002).

It is important to point out that auditory ERPs averaged across NREM sleep, especially NREM-2, contain neural activations of K-complexes, a sleep specific potential (Perrin, García-Larrea, Mauguière, & Bastuji, 1999) and sleep spindles (Berger, 1933; Loomis,, Harvey & Hobart, 1935). K-complexes occur only during NREM sleep and consist of positive and negative ERP deflections (N350, N550, and P900). The negative deflections are by far the largest activations that can be measured for humans (Bastien & Campbell, 1992; Colrain & Campbell, 2007). K-complexes were first described in 1939, and have been reported to be responses to external stimuli (Loomis, Harvey & Hobart, 1939), as well as spontaneous activations that occur independent of sensory information (Davis, Davis, Loomis, Harvey & Hobart, 1939). The function of K-complexes are still not fully understood, however they are thought to indicate a state of arousal (e.g., Halasz, 1993; Roth, Shaw & Green, 1956), or to

reflect events that protect sleep, that is states of reduced arousal (e.g., Nicholas, Trinder & Colrain, 2002; Peszka & Harsh, 2002). Sleep spindles are transient potentials specific to NREM sleep, and in the EEG signal visible as bursts of oscillatory activity with a frequency of 12 Hz to 14 Hz (De Gennaro & Ferrara, 2003). Sleep spindles are generated in the thalamus and thought to play a crucial role in the induction, regulation, and maintenance of sleep (e.g., Steriade, McCormick & Sejnowski, 1993; Urakami, 2008; Astori, Wimmer & Lüthi, 2013). That is, they promote deeper sleep, and their activity seems to be crucial for a controlled information flow within the thalamocortical network. Spindles are thought to induce membrane hyper-polarization which leads to a reduced synaptic responsiveness, and consequently to an interrupted flow of information (Steriade, McCormick & Sejnowski, 1993, Velluti, 1997;.De Gennaro & Ferrara, 2003). That means sensory information that occurs simultaneously with sleep spindles is less likely to arouse or awake a sleeping person and might not be passed along the thalamocortical network. Additionally, increased synchronized activity or discharge within the thalamocortical network is thought to be a reason for the increased ERP amplitudes during NREM sleep, especially NREM-3 (Velluti, 1997).

1.5. Research background

1.5.1. General information

Research on sleep indicates that environmental information can be received and to certain extent processed (see above). However far too little is known about which information is processed and whether processing steps performed during sleep are comparable to those performed during wakefulness. The research presented in this thesis aims to gain more insights

into the effects of sleep on auditory information processing, more precisely, on the cortical processing of auditory frequency information. This could not only help to gain a better understanding of how the brain processes auditory frequency information, but also help to better understand the differences in the functioning of our brains during sleep relative to wakefulness. In my thesis I tested the effects of sleep on the processing of frequency information directly and indirectly. The direct approach consisted of night recordings in which the processing of frequency information was measured during whole night sleep. The indirect measure is based on the application of a training paradigm by Pantev and colleagues, who demonstrated that listening to notched music, (i.e., music from which certain frequencies have been removed) for an extended period of time reduces the cortical processing of the removed frequencies (e.g., Okamoto, Stracke, Stoll & Pantev, 2010; Pantev, Wollbrink, Roberts, Engelien & Lütkenhöner, 1999). I applied this training paradigm during whole night sleep to test the effects of sleep on frequency processing indirectly. That is, changes in cortical frequency processing could be detected after the 'sleep training' would be an indication that profound frequency processing takes places during sleep. To assure that we are able to perform this training paradigm correctly, I performed an additional study in which the training paradigm was performed during wakefulness. The three main research questions that have been addressed in my thesis are: (1) Effects of notched music listening on the cortical processing of frequencies within and below the music notch in awake participants. (2) Whether responses specific to auditory frequency processing can be measured during whole night sleep, and (3) whether the sleeping brain remains perceptive enough throughout whole night sleep to induce cortical changes in auditory frequency processing. Before

presenting each of the three studies, this introduction will be completed by giving a brief overview about three concepts that are relevant for the performed research.

1.5.2. Frequency specificity, Adaptation, and Amplitude modulation

The cortical response specific to the processing of one frequency relative to others is called *Frequency specificity* and can be measured via amplitude modulation, or by comparing the cortical responses of simultaneously or subsequently presented frequencies (Ross, Draganova, Picton & Pantev, 2003). Adaptation designs are based on a subsequent frequency presentation. The term adaptation refers to a decrease in evoked neural activity after the repeated or prolonged presentation of a stimulus. The effect is fairly stable and has been demonstrated across senses and in numerous experimental conditions. Adaptation is just one of many terms that can be found in the literature to describe this effect. Names like ‘repetition suppression’ or ‘neural priming’ are used amongst others (Grill-Spector, Henson & Martin, 2006). The underlying neural mechanisms of adaptation are still not fully understood, however a number of models have been proposed (see Grill-Spector, Henson & Martin, 2006). Related to frequency specificity, an adaptation response is generated by the repeated or prolonged presentation of one frequency (adapter tone). The subsequent presentation of a second frequency (probe tone) will generate an adaptation release response. This frequency specific adaptation release response is based on the activation of unadapted neurons. A strong adaptation response, and therefore a strong adaptation release response, can be induced when using long adapter tones, and short inter-stimulus intervals between adapter and probe tone (Lanting, Briley, Sumner & Krumbholz, 2013). Furthermore it has been shown that adaptation decreases with increasing frequency difference between adapter and probe tone

(Briley & Krumbholz, 2013; Butler, 1968). The adaptation test applied in this thesis is based on a prolonged presentation of an adapter frequency which is followed by a probe frequency. Both frequencies are presented within one stimulus (two-tone stimuli), with the probe frequency being presented continuously (silent-free) after the adapter frequency. The frequency specific response to these stimuli was ascertain via the vertex-potential (N1-P2) of the probe tone response.

Amplitude modulation, the second of the above mentioned approaches to measure frequency specific responses, refers to the effect that amplitude modulated sounds evoke a neural response that follows the envelope of the modulation frequency (Kuwada, Batra & Maher, 1986). This response can be considered as an auditory steady state response (Stapells, Linden, Suffield, Hamel & Picton, 1984), with differing generators, based on the applied modulation frequency. Lower modulation frequencies (25 - 55 Hz) are thought to originate in the cortex, higher modulation frequencies (100 - 400 Hz) are thought to generate in the midbrain (Kuwada, Batra & Maher, 1986). In contrast to ERPs, which are transient evoked potentials (Crowley & Colrain, 2004), the auditory steady state response is considered a sustained response or potential (Plourde, 2006). Amplitude modulation measures have gained tremendous interest in auditory research and clinical settings due to its frequency specificity and the close relation between the cortical measure and the results of behaviourally obtained auditory threshold estimations. A 40 Hz amplitude modulation is preferable when testing awake subjects, as this modulation frequency will evoke the strongest cortical responses (Kuwada, Batra & Maher, 1986; Picton, Skinner, Champagne, Kellett & Maiste, 1987). A modulation frequency of 80 Hz is suggested when testing the cortical processing of frequency information in sleeping subjects, as activations in the midbrain are less state

dependent (Levi, Folsom & Dobie, 1993). Responses to amplitude modulated sounds can be ascertained via frequency analyses, like fast Fourier analyses, of the EEG recording (Picton, John, Dimitrijevic & Purcell, 2003). The amplitude modulation test employed in this thesis has been applied to test frequency processing in awake subjects and consisted of pure tones that have been presented with a 40 Hz amplitude modulation (see below article 1).

In the following three studies focussing on the processing of frequency information during sleep and wakefulness, will be presented in more detail. This research was supported by the National Science and Engineering Council of Canada, the NSERC-Create program in Auditory Cognitive Neuroscience, and by the Fonds de recherche du Québec – Santé.

CHAPITRE 2:

Article 1 (in preparation)

The effect of notched music listening

Ramona Kaiser and Marc Schoenwiesner

2.1. Introduction

A number of studies suggest that listening to 'Notched music' for a short period of time can alter the cortical processing of frequencies within the frequency range of the music notch. 'Notched music' refers hereby to music in which a specific frequency range has been removed via notch- or band-pass filter. Pantev, Wollbrink, Roberts, Engelien, and Lütkenhöner tested this idea in 1999 for the very first time. The authors asked eight normal hearing participants to listen to notched music for three hours per day on three subsequent days. Each day participants performed two MEG sessions, one before and one after the three hours of music listening. During each MEG session two stimuli were presented, a test stimulus whose frequency corresponded to the center of the music notch, and a control stimulus with a frequency 1 octave below the test stimulus (music notch: 700 Hz - 1300 Hz, test stimulus 1000 Hz, control stimulus 500 Hz). Effects of notched-music listening were ascertained via changes in the strength of the N1m component for both stimuli within and across test days. Results indicate a decreased cortical activation for the test stimulus after the second and third day of notched-music listening, but no differences in the processing of the control stimulus.

The authors propose that the reduced neural activity of the tested within-notch frequency is based on lateral inhibition. Notched-music listening activates all neurons sensitive to the presented music frequencies. The activation of neurons tuned to frequencies of the music notch are actively suppressed by the surrounding neurons inducing over time a functional deafferentation (Okamoto, Stracke, Stoll & Pantev, 2010; Pantev, Okamoto & Teismann, 2012).

In a second study Okamoto, Stracke, Stoll, and Pantev (2010) tested the effects of notched-music listening on participants with tonal tinnitus. Tinnitus can be described as an auditory phantom sensation which has been related to peripheral hearing loss and a related maladaptive reorganization in the auditory cortex (Jastreboff, 1990; Eggermont & Roberts, 2004). Tonal tinnitus refers hereby to phantom sounds that resemble a whistling or ringing sound (e.g., Meikle, Vernon, & Johnson, 1984). Okamoto et al., (2010) asked their participants to listen to notched music daily for 12 months. The music notch was adjusted to each participants' tinnitus perception by centering the music notch around the individual tinnitus frequency. All participants performed three MEG sessions, one before, one after 6 months of music listening and one at the end of the music listening period. As in the study by Pantev et al. (1999) two sound stimuli, a test stimulus and a control stimulus, were presented throughout each MEG session. The test frequency corresponded to each participants' tinnitus frequency. The control stimulus was, constant across participants, a 500 Hz tone. Stimuli were presented as partly amplitude modulated pure tones (i.e., a 40 Hz amplitude modulation was introduced 300 ms after stimulus onset). Such stimuli allow the recording of two auditory potentials, the auditory steady-state response (ASSR), and the transient N1-P2 component (Engelien, Schulz, Ross, Arolt, & Pantev, 2000). Effects of notched-music listening were ascertained by

comparing N1m and ASSR measures across test sessions. The authors report a significant effect of notched-music listening for the test frequencies with a decreased source strength for N1m and ASSR measures after 6 months, and after 12 months of notched music listening.

In 2011 a tinnitus treatment, the Tailor-Made Notched Music Training (TMNMT), was proposed by Teismann, Okamoto, and Pantev based on the above mentioned results (see also Pantev, Okamoto & Teismann, 2012). The authors showed a decreased cortical activation of participants' tinnitus frequency after 6 hours of notched-music listening on 5 subsequent days. The effects of the suggested tinnitus treatment were tested further in a number of follow up studies, all performed in the group around Pantev. It has been shown, for example, that already 3 days of TMNMT can reduce tinnitus related cortical activation (Stein et al., 2015a) and that the width of the music notch has no impact on the TMNMT outcome (Wunderlich et al., 2015).

All of the above mentioned studies support the claim that notched-music listening alters the processing of frequencies within the notched frequency range. However despite the respectable number of studies surprisingly little is known about the effect of notched-music listening on the processing of frequencies within and outside the music notch. All mentioned studies tested the neural activity of only two frequencies, one within and one below the music notch range. The within-notch frequency corresponded always to the center frequency of the music notch. The below-notch frequency remained, across all studies, a 500 Hz stimulus independent of the applied notch range. The small number of test frequencies and the restricted relation between test and control frequencies and the notch range do not allow for a systematic analysis of the effects induced by notched music listening.

The aim of the present study was to gain a better understanding of the effects of notched-music listening on the processing of frequencies within and below the music notch. Test frequencies, systematically distributed within and below the notch, have been presented to participants before and after a period of notched music listening. Changes in frequency processing have been ascertained via two measures. An adaptation test which measures changes in the frequency specific response, and an amplitude modulation test which measures changes in the ASSR. The latter test was adopted from the test design used in almost all of the above mentioned studies. The two tests have been applied to compare both approaches, adaptation and amplitude modulation, for the measure of cortical frequency processing. Based on the outcomes of this study, the most promising test will be used in the remaining two studies of this thesis.

2.2. Methods

The study consisted of three parts, a music listening period and two EEG sessions, one performed before and one directly after the music listening period. Each EEG session consisted of two EEG tests, an Amplitude modulation test (AM) and an Adaptation test (AD). The order of the two EEG tests varied between participants, but remained constant across EEG sessions. Half of the participants performed the Adaptation test first (AD1), the remaining half performed the Amplitude modulation test first (AD2), during each test session.

2.2.1. Participants

A total of 16 persons (7 male and 9 female), with an average age of 27 years (age range 23 – 36 years), provided written informed consent, and participated as paid volunteers in the present study. All participants had normal or corrected-to-normal vision and did not report a history of hearing disorders or neurological diseases. Participants were screened for normal hearing (i.e., hearing thresholds below 20 dB HL for octave-spaced frequencies between 125 Hz and 8000 Hz). The study was in accordance with the Declaration of Helsinki and approved by the ethics committee of the Faculty of Arts and Sciences of the University of Montreal, Quebec/Canada. All testing was performed at the International Laboratory for Brain, Music and Sound Research (BRAMS) in Montreal, Quebec/Canada.

2.2.2. Stimuli and Materials

2.2.2.1. Music listening period

Each participant provided their own music in MP3 quality (sampling rate 44.1 kHz, 16 bit, stereo). A notch filter with cutoff frequencies at 600 Hz and 1200 Hz, was applied to each music file using SOX (sox.sourceforge.net). Participants could receive new notched music at any time during the music listening period. During the listening period participants were asked to respond to a daily questionnaire to collect information related to the music listening like, for example, the daytime and duration participants had listened to the notched music, the sort of headphone that has been used, and whether participants listened to the music actively or passively (i.e., whether the music listening was an exclusive activity or performed additionally to other activities).

2.2.2.2. EEG tests

In both EEG tests, AM and AD, the same stimuli frequencies were used. The frequencies were selected based on the following criteria: (1) The filter edge frequency has to lie outside the critical bandwidth of the lower cut-off frequency of the notch filter (600 Hz). The critical bandwidth was calculated based on equivalent rectangular bandwidth (ERB) method:

$$\mathbf{ERBN = 24.7(4.37 * frequency + 1)}$$ (Moore, 2008b)

The critical bandwidth for the lower cut-off frequency was estimated around 510 Hz, and the filter edge frequency was set to 500 Hz. (2) Half of the test frequencies lie below, and the remaining half lie within the frequency range of the music notch. (3) Test frequencies are equally spaced above and below the edge frequency with a distance of 0.5 octave and 1 octave (see Figure 2.1). The resulting test frequencies have been: 250 Hz, 354 Hz, 707 Hz and 1000 Hz.

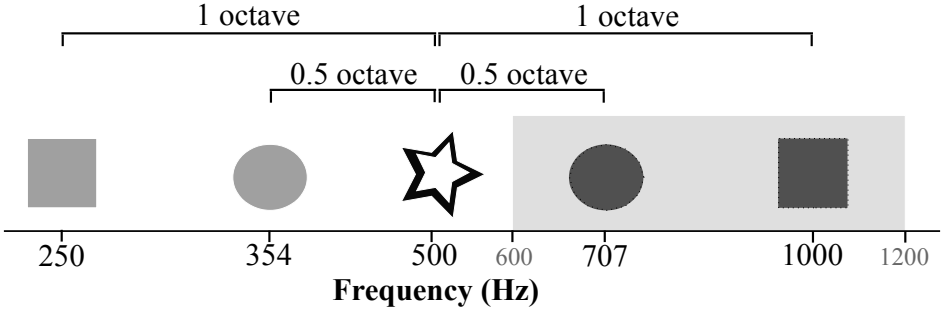


Figure 2.1: **Graphical display of frequency composition**. Grey shaded area represents the frequency range of the music notch (upper and lower cut-off frequency of the notch filter are shown as grey numbers). The edge frequency, represented as a star, lies more than one critical bandwidth below the lower cut-off frequency. Test frequencies are shown as squares (1 octave distance to edge frequency) and circles (0.5 octave distance to edge frequency). Test frequencies within the frequency range of the music notch are displayed in darker grey, test frequencies below the music notch are displayed in lighter grey.

2.2.2.2a Adaptation test

Four sound stimuli were presented during the adaptation test. Each sound stimulus consisted of two merged pure tones, a 500ms long adaptation tone followed by 100 ms long probe tone. The frequency of the adaptation tone corresponded to the edge frequency (500 Hz) and remained constant across stimuli. The frequency of the probe tone varied between the four sound stimuli and corresponded to the test frequencies (250 Hz, 354 Hz, 707 Hz, and 1000 Hz). Each stimulus lasted 600 ms including a 10ms cosine fade-in and fade-out.

2.2.2.2b Amplitude modulation test

Five sound stimuli were presented in the Amplitude modulation test. Each sound stimulus consisted of a 1000 ms long pure tones with a 40 Hz-amplitude modulation for the last 700 ms. The stimuli frequencies included the four test frequencies as well as the edge frequency. All sound stimuli had a 10ms cosine fade-in and fade-out.

2.2.3. Design

Each EEG test followed a mixed within-between subject design with three within-subject variables and one between-subject variable. The within-subject variables have been '*Test session'* (pre-test and post-test), '*Notch range*', which comprises the test frequencies below and within the frequency range of the music (below-notch and within-notch range), and '*Test frequencies',* which comprises the test frequencies presented in each EEG test. The between-subject variable '*Test order'* indicates the test order of the performed EEG tests (AD1 and AD2). The effect of notched-music listening was quantified both EEG tests by

comparing differences between pre- and post-test measurements for both notch ranges and the presented test frequencies.

2.2.4. Procedure and Data acquisition

For the music listening period participants were asked to listen to their notched music for at least 3 hours per day on at least 12 subsequent days. EEG recordings were performed in a soundproofed faraday room. Participants were seated in a comfortable chair in about 100 cm distance to a shielded Sony G520 CRT screen on which a muted movie with subtitles was presented throughout the EEG recordings (screen refreshment rate 60 Hz, screen resolution 1400 x 1050 pixels). Auditory stimuli were presented to both ears via Etymotic ER-1© inserts with ER1-14a eartips. Stimulus presentation was implemented using Matlabⓒ and a signal processing system by Tucker-Davis Technologiesⓒ (RX6). The EEG signal was recorded via a BioSemi ActiveTwo system (BioSemi, Amsterdam, The Netherlands) using elastic caps with 64 EEG electrodes plus 6 external electrodes. The external electrode were positioned at the mastoids, below the left eye to measure vertical electrooculogram (EOG), lateral to each eye to measure horizontal EOG, and one reference electrode at the tip of the nose. Signals were recorded with a sampling rate of 1024 Hz using BioSemi ActiView software. During test sessions participants had no test task other than to to watch the movie (passive EEG recordings). Participants were asked to remain relaxed and to avoid any unnecessary head- or body movements throughout the recording.

2.2.4.1. Adaptation test

Stimuli were presented in pseudorandom order, pre-conditioned to alternate between test frequencies below and within the frequency range of the music notch. Stimuli were presented with a jittered inter stimulus interval ranging from 450 ms to 500 ms. The sound level of both stimulus tones, adapter tone and probe tone, were adjusted to a sound level of 80 dBA SPL. Throughout one test session each of the four stimuli was repeated 550 times (total of 2200 trials). One test session lasted for 39 minutes.

2.2.4.2. Amplitude modulation test

Stimuli in the Amplitude modulation test were presented in pseudorandom order, pre-conditioned to alternate between frequencies below and within the frequency range of the music notch. Stimuli were presented with a jittered inter stimulus interval ranging from 500 ms to 550 ms. All five stimuli were presented with a sound level of 80 dBA SPL. Throughout one test session each of the five sound stimuli were repeated 400 times (total of 2000 trials). One test session lasted 51 minutes.

2.2.5. Data processing

2.2.5.1. Music listening period

Participant's individual exposure time was calculated by averaging the reported daily hours of notched-music listening (mean exposure time). As nearly no participant reported active listening, a separate calculation of exposure time for active and passive music-listening was not performed.

2.2.5.2. Adaptation test

Each continuous EEG recording was preprocessed using the EEGlabⓒ toolbox (Delorme & Makeig, 2004) and ERPlabⓒ toolbox (Luck & Lopez-Calderon, 2010) in combination with Matlabⓒ. The preprocessing steps have been as follows: (1) The signal was re-referenced to the averaged mastoids signal, (2) resampled to a sample rate of 256 Hz, and (3) filtered applying basic FIR (finite impulse response) filters with a lower edge frequency of 1 Hz and a higher edge frequency of 30 Hz. (4) An independent component analysis (ICA), applying the runica algorithm, was performed to detect and remove blinks and eye-movement related artifacts in the EEG signal (Jung et al., 2000; Bell & Sejnowski, 1995). In preparation for the ICA analyzes noisy samples and channels were manually removed from the data set. (5) Following the ICA, external electrodes were removed, the continuous EEG recording was epoched with epochs ranging from 200 ms prior probe tone onset (i.e., 300 ms after stimulus onset) to 200 ms post stimulus offset, and epochs were baseline corrected relative to the 200 ms interval prior the probe tone onset. (6) EEGlabⓒ's automatic artifact rejection for epoched data was performed with the initial threshold of 5 standard deviations and a threshold limit of 1000 microVolt. In average 13% of epochs (range: 1% to 29% of epochs) were rejected by the end of the signal preprocessing, resulting in an average of 478 trials per stimulus. Finally, (7) missing EEG electrodes were interpolated and (8) average event related potential (average ERPs) were calculated for each participant and probe tone frequency.

In preparation for data analyses participants' average ERP signals were used to ascertain the N1-P2 activation for each probe tone and test session. First, the root mean square (RMS) of the average ERP signals was calculated across channels for each sample point

within a time window that comprised the N1-P2 deflections. The sample range of this window was estimated based on the grand average and ranged from +67 ms to +270 ms relative to the probe-tone onset (see Figure 2.2). Secondly, the mean 'area under the curve' (m-AUC) was calculated from the RMS-signal as a measure of global cortical activation for the N1-P2 component (Ponton, Don, Eggermont & Kwong, 1997). The resulting m-AUC values were z-score normalized for each participant across stimuli and test sessions.

2.2.5.3. Amplitude modulation test

The continuous EEG recordings of the amplitude modulation test were processed following the same first seven steps as described for the Adaptation test (see above). The applied FIR filter in this test had a lower edge frequency of 1 Hz and a higher edge frequency of 40 Hz. Subsequently to step 7, the epoched signal was imported into Letswave 6, a matlab toolbox by André Mouraux, (http://nocions.github.io/letswave6), to perform the final processing steps. In Letswave (1) average ERPs were calculated for each participant and stimulus frequency. (2) Each average ERP was baseline corrected applying a Frequency spectrum signal to noise ratio (SNR) transform. (3) Fast Fourier Transform (FFT) analysis were performed to ascertain cortical responses to the 40 Hz amplitude modulation. (4) Mean FFT values were calculated for each stimulus, test session, and participant based on the maximum peak response between 38 Hz and 42 Hz across all channels (see Figure 2.3). In preparation for data analyses mean FFT values were z-score normalized for each participant across stimuli and test sessions.

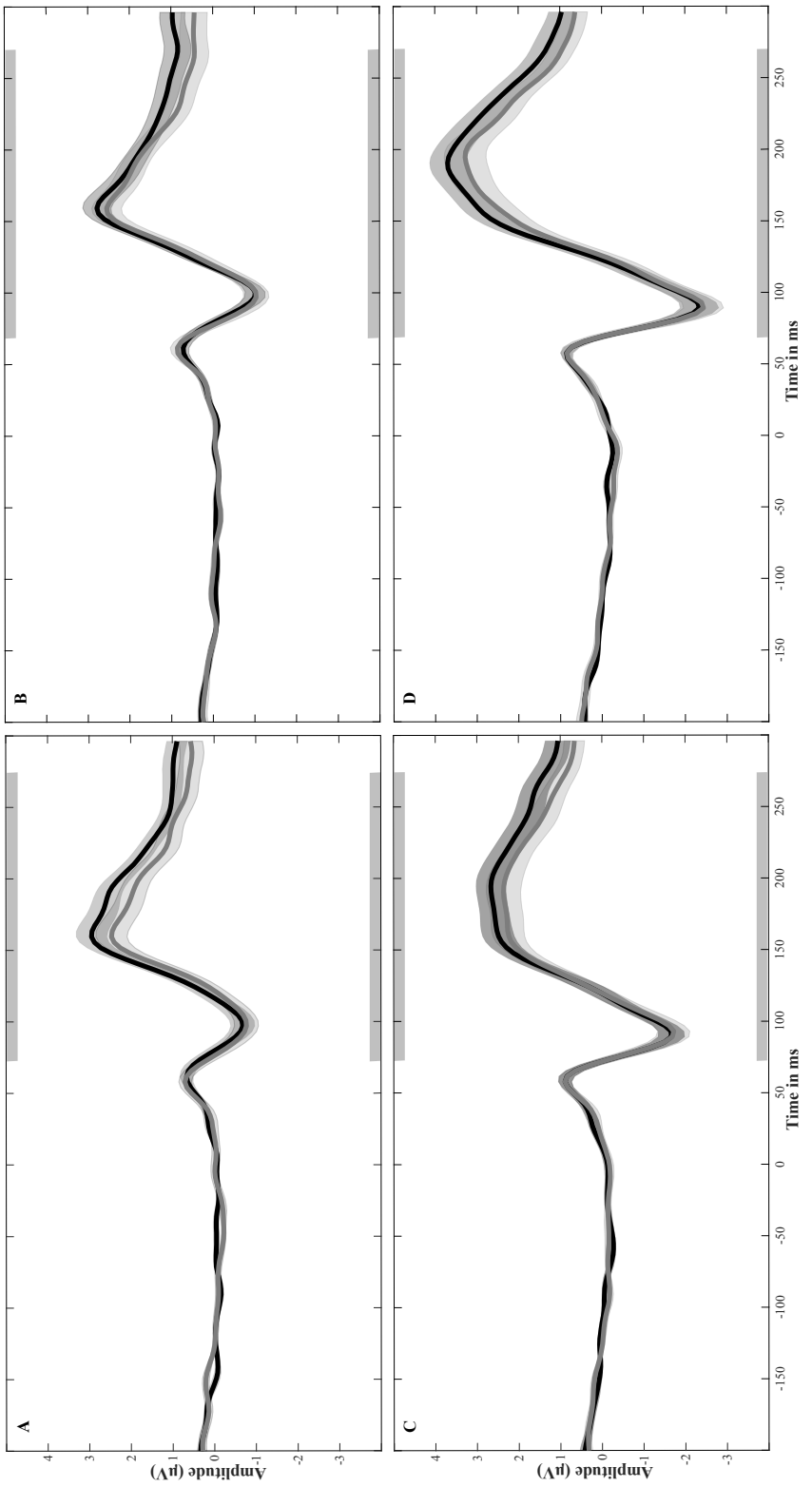
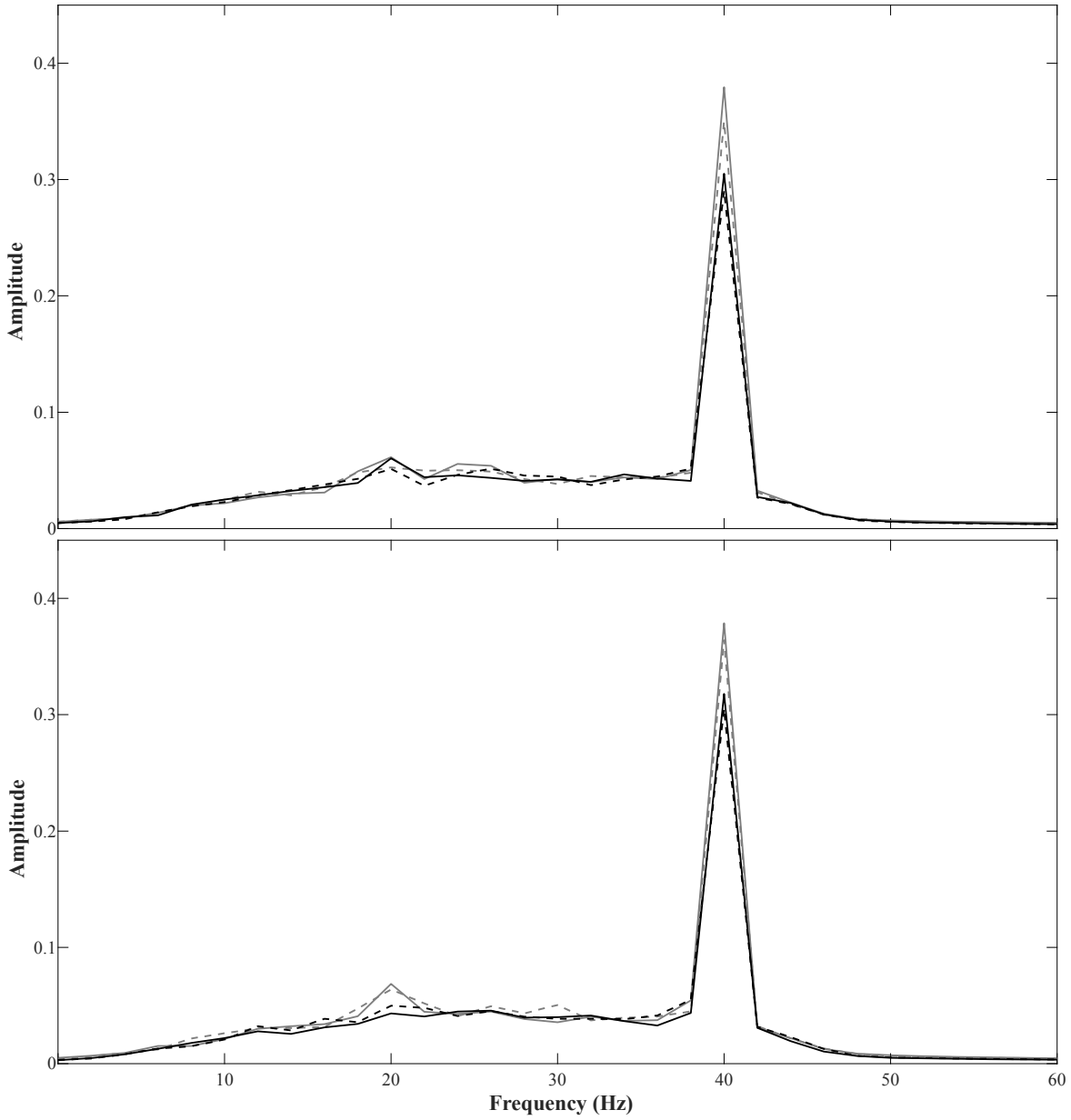


Figure 2.2: **Adaptation test: Grand average ERPs**. Grand average ERPs for each probe tone presented during the Adaptation test. Grey shaded squares indicate range of the N1-P2 window used to calculate the AUC values. Shaded areas indicate the standard error across participants. Pre-test results are shown in light grey, post-test results are shown in dark grey. **A:** Response for the 250 Hz tone. **B:** Response for the 354 Hz tone. **C:** Response for the 707 Hz tone. **D:** Response for the 1000 Hz tone.

Figure 2.3: **Amplitude modulation test: Mean FFT**. Mean FFT values for test frequencies of the amplitude modulation test. Pre-test results are shown as dashed lines, post-test results are shown as solid lines. *Upper plot:* Test frequencies of below-notch range. In lighter grey responses for 250 Hz tone, in darker grey responses for 354 Hz tone. *Lower plot*: Test frequencies of within-notch range. In lighter grey responses for 707 Hz tone, in darker grey responses for 1000 Hz ton.



2.3. Analyses and Results

The effect of notched-music listening was ascertained by analyzing differences in cortical activations between pre-test and post-test recordings for test frequencies below and within the music notch (notch range activations), as well as for each test frequency separately (frequency activations). The same analyzes were applied to both EEG tests, adaptation test and amplitude modulation test. All results reported in this sections have been adjusted for multiple comparisons (i.e., Bonferroni correction).

2.3.1. Music listening

Analyzes of the daily music listening questionnaires revealed that participants have listened in average to 34 hours of notched music throughout the music listening period (range 22 to 47 hours), and in average 3.2 hours of notched music listening per day (range: 2.4 to 4 hours). Results of an independent t-test showed no differences in the reported hours of music listening between the two participant groups which have been created due the performed test order ($t_{(14)} = -.835$, $p = .418$, $r = .218$), where r represents an effect size measure that is calculated, following Field (2009), as $\text{sqrt}(t^2/(df + t^2))$.

2.3.2. Adaptation test

2.3.2a. Notch range activations

Notch range activations represent the combined responses of test frequencies within one notch range. Each notch range activation is based on the difference between the frequencies of one notch range and has been calculated, for each notch range and test session,

by subtracting the 1-octave tone response from the related 0.5-octave tone response (*below-notch*: 250 Hz - 354 Hz; *within-notch*: 1000 Hz - 707 Hz). Subsequently the obtained post-test values were subtracted from the pre-test values to estimate changes in activation across test sessions and the resulting values have been used in the following analyzes. Upon inspection of the data, an outlier was detected for the within-notch measure with a mean value more than two standard deviations apart from the sample mean (see Figure 2.4). The data of this participant were excluded from all adaptation test analyses. The distribution of both notch ranges were tested for normality applying Shapiro-Wilk tests. Both distributions were found to be normally distributed (*below-notch*: $W_{(15)} = .965$, $p = .779$; *within-notch*: $W_{(15)} = .908$,$p = .124$). The use of parametric tests in the following analyzes is therefore adequate. Subsequently, independent t-tests were performed to test the effect of test order, which revealed no significant difference between participants who performed the Adaptation test first or last for both distributions (*below-notch*: $t_{(13)} = 1.425$, $p = .178$, $r = .368$; *within-notch*: $t_{(13)} = 1.012$, $p = .330$, $r = .270$). The variable Test order will therefore be ignored in the following analyzes.

The changes in notch range activation across test sessions was analyzed for each notch range applying one-sample t-tests with the test value 0. Results show significant differences between pre- and post-test session for both notch ranges (*below-notch*: $t_{(14)} = -4.325$, $p < .001$, $r = .756$, *within-notch*: $t_{(14)} = -3.023$, $p < .01$, $r = .628$,). For both distributions, a significant increase in activation differences was found for post-test measures relative to pre-test measures, indicating a change in the processing of frequencies due to the notched-music listening period (see Figure 2.5).

Figure 2.4: **Adaptation test: Participant data for within-notch range across test sessions**. Participants mean activation for the within-notch range are shown as stars. Participant mean is shown as grey dashed line. The grey shaded area indicates the range of 2 standard deviations around the participant mean. The outlier, which is more than two standard deviations apart from the sample mean has been removed from all analyzes of the adaptation test.

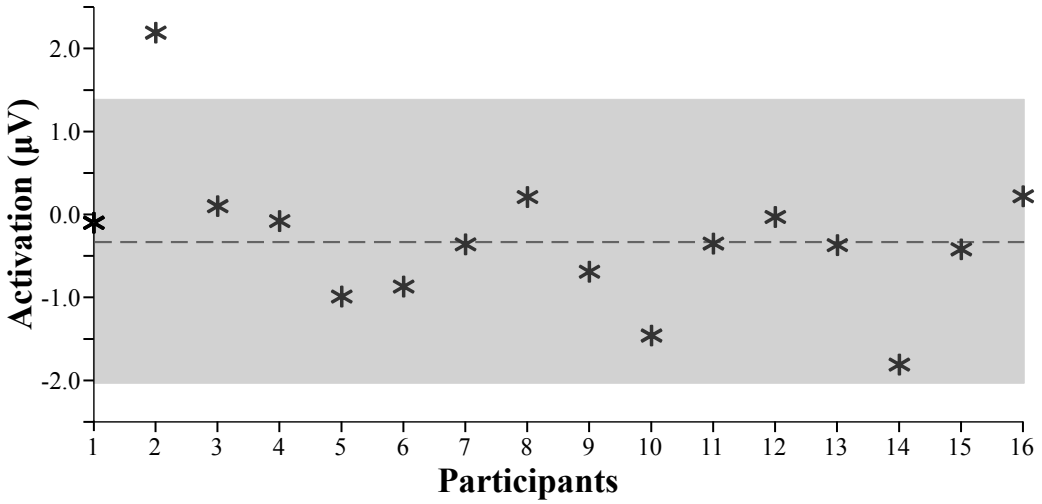
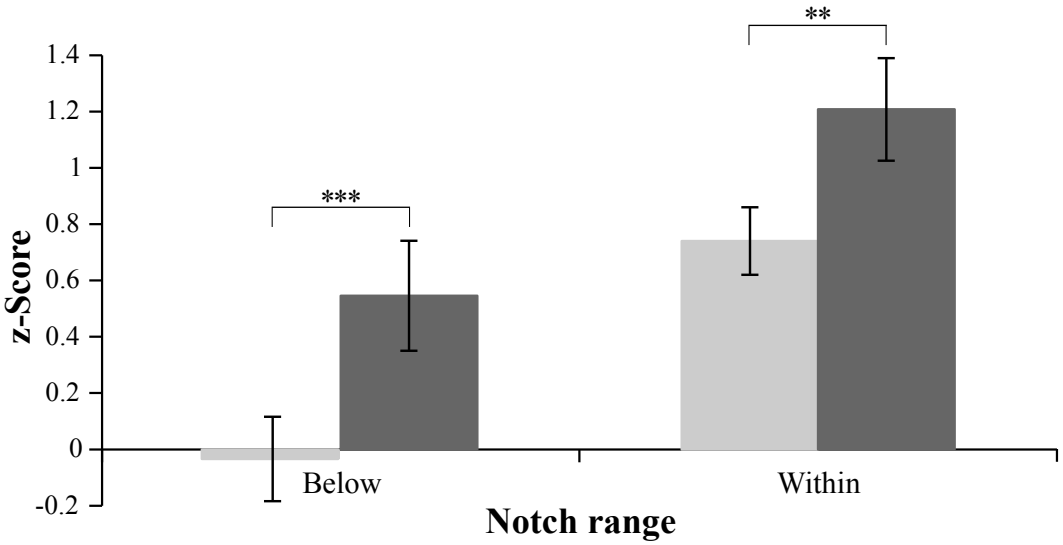


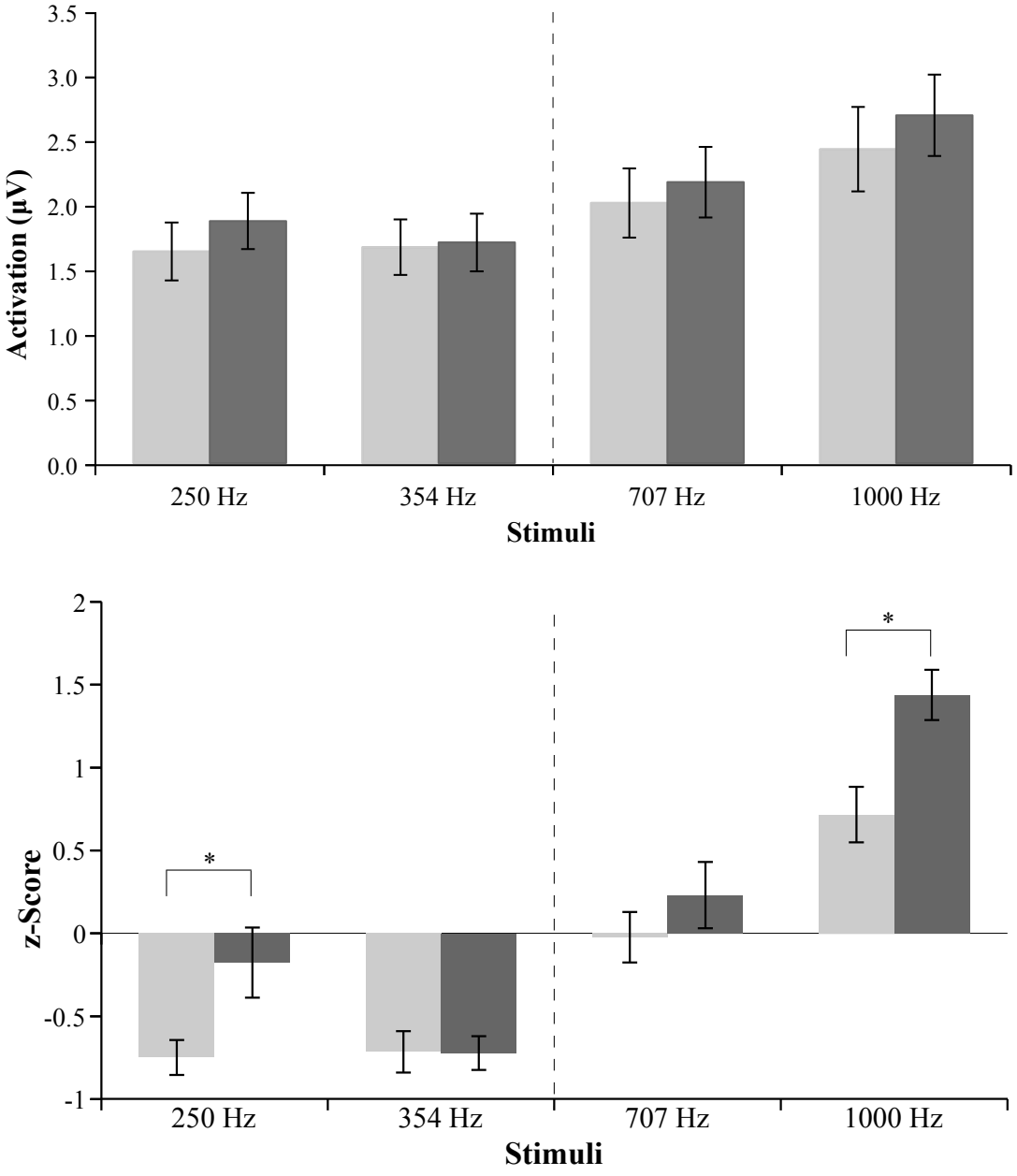
Figure 2.5: **Adaptation test: Notch range activations across test sessions.** Notch range activations represent mean differences between frequencies within each notch range per test session. Pre-test values are shown in light grey, post-test values are shown in darker grey. Error bars indicate standard error across participants. Significance levels of performed analyzes (one-sample t-test: Notch range activation across test sessions) are indicated as follows: *** p < .001; ** p < .01; * p < .05.



2.3.2b Frequency activations

In a second set of analyses the effect of notched-music listening was ascertained for each of the presented frequencies. The difference between frequency responses across test sessions was calculated for each test frequency by subtracting its post-test activation from its pre-test activation. The resulting values have been used in the following analyzes. Shapiro-Wilk tests were applied to for violations of the normality assumption. Results indicate that all distributions are normally distributed (*250Hz*: $W_{(15)} = .928$, $p = .251$; *354Hz*: $W_{(15)} = .937$, $p = .351$; *707Hz*: $W_{(15)} = .944$, $p = .433$; *1000Hz*: $W_{(15)} = .964$, $p = .760$). Independent t-tests were performed to test the effect of test order. Results reveal no significant differences between the two participant groups (*250Hz*: $t_{(13)} = 1.469$, $p = .166$, $r = .377$; *354Hz*: $t_{(13)} = .483$, $p = .637$, $r = .133$; *707Hz*: $t_{(13)} = .320$, $p = .754$, $r = .088$; *1000Hz*: $t_{(13)} = .905$, $p = .382$, $r = .243$). The variable test order will therefore be ignored in the following analyzes. Differences between pre- and post-test activations were analyzed for each test frequency applying one-sample t-tests with the test value 0. Results indicate a significant difference between pre- and post-test activations for test frequencies 1 octave below and 1 octave above the edge frequency with a significant increase in activation for the post-test relative to the pre-test for both test frequencies (*250Hz*: $t_{(14)} = -2.899$, $p < .05$, $r = .612$; *1000Hz*: $t_{(14)} = -2.633$, $p < .05$, $r = .575$). No significant difference between pre- and post-test activations were found for test frequencies 0.5 octave below or 0.5 octave above the edge frequency (*354Hz*: $t_{(14)} = .037$, $p = .971$, $r = .010$, *707Hz*: $t_{(14)} = -.900$, $p = .383$, $r = .234$; see Figure 2.6).

Figure 2.6: Adaptation test: Frequency activations. Frequency responses across test sessions. Pre-test values are shown in light grey, post-test values are shown in darker grey. Frequencies left of the dotted line lie below the music notch, frequencies right of the dotted line lie within the music notch. *Upper plot* shows mean frequency responses before z-score transform. *Lower plot* shows z-normalized data (data used for analyzes). Error bars indicate standard error across participants. Significance levels of performed analyzes (one-sample t-test: Frequency activations across test sessions) are indicated as follows: *** p < .001; ** p < .01; * p < .05.



2.3.3. Amplitude modulation test

Following the analyzes of the Adaptation test, the effect of notched-music listening was ascertained by analyzing differences between pre- and post-test session for both notch ranges activations, as well as for each test frequency.

2.3.3a. Notch range activations

The two notch range distributions were tested for normality applying Shapiro-Wilk tests, and both were found to be normally distributed (*below-notch*: $W_{(16)} = .976$, $p = .929$; *within-notch*: $W_{(16)} = .941$, $p = .359$). The effect of test order was analyzed via independent t-tests. Results reveal a significant effect of test order for the below-notch range ($t_{(14)} = -2.974$, $p < .01$, $r = .622$), indicating differences in the measures of the below-notch range between participants who performed the amplitude modulation test first (AD2) or last (AD1). No effect for test order was found for the within-notch range differences ($t_{(14)} = -1.272$, $p = .224$, $r = .322$). Due to the significant effect of test order, found for below-notch range measures, analyzes for this measure will be performed individually for each group. One-sample t-tests with the test value 0 were performed to analyze differences across test days for each notch range. The within-notch range difference was analyzed across all participants ($N = 16$). The below-notch range difference was analyzes with two separate t-tests, one for each group ($n = 8$). Results reveal a significant difference for the below-notch range for group AD2, with significant increased frequency differences in post-test measures relative to pre-test measures ($t_{(7)} = 5.182$, $p < .001$, $r = .891$). No significant difference between pre- and post-test were

found for group AD1 for the below-notch range ($t_{(7)}$ = -.449, p = .667, r = .167), nor for the within-notch range across test groups ($t_{(15)}$ = -.094, p = .927, r = .024; see Figure 2.7).

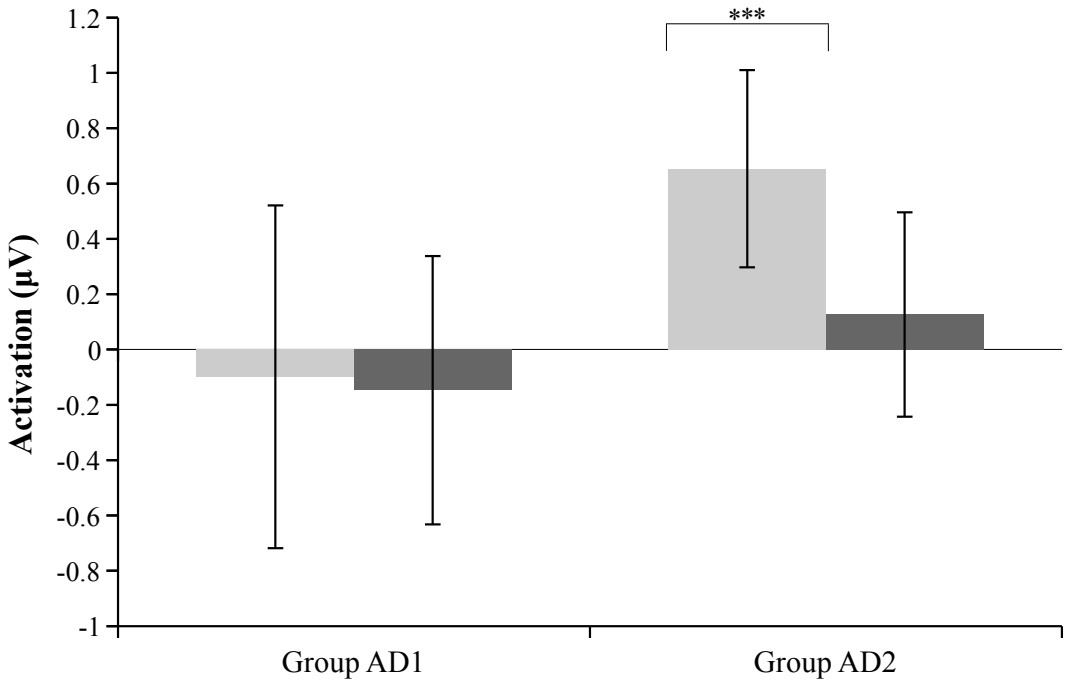


Figure 2.7: **Amplitude modulation test: Notch range differences across test sessions per group.** Differences between notch range activations across test sessions for each participant group (AD1: Participants performed adaptation test first in both test sessions; AD2: Participants performed adaptation test last in both test sessions). Differences for the below-notch range are shown in lighter grey, differences for the within-notch range are shown in darker grey. Error bars indicate standard error across participants. Significance levels of performed analyzes (one-sample t-test: Notch range activation across test sessions) are indicated as follows: *** p < .001; ** p < .01;* p < .05.

2.3.3b Frequency activations

Subsequently, differences between pre-test and post-test activations were analyzed for each test frequency. As for the adaptation test, the post-test response of each frequency was subtracted from the related pre-test response to ascertain changes in frequency processing across test sessions. The distribution of each frequency was tested for normality applying Shapiro-Wilk tests, and every distribution was found to be normal (*250Hz*: $W_{(16)} = .908$, $p = .106$; *354Hz*: $W_{(16)} = .977$, $p = .933$; *707Hz*: $W_{(16)} = .947$, $p = .448$; *1000Hz:* $W_{(16)} = .951$, $p = .503$). Results of independent t-tests on the effect of test order revealed significant effects for all but the lowest test frequency (*250Hz*: $t_{(14)} = .489$, $p = .632$, $r = .130$; *354Hz*: $t_{(14)} = 2.274$, $p < .05$, $r = .519$; *707Hz*: $t_{(14)} = 2.770$, $p < .05$, $r = .595$; *1000Hz*: $t_{(14)} = 2.423$, $p = < .05$, $r = .544$). An additional analyses on the frequency responses during the pre-test session only shows no differences between both groups (*250Hz*: $t_{(14)} = -.026$, $p = .980$, $r = .007$; *354Hz*: $t_{(14)} = 1.419$, $p = .178$, $r = .355$; *707Hz*: $t_{(14)} = 1.760$, $p = 0.100$, $r = .426$; *1000Hz*: $t_{(14)} = 1.025$, $p = .323$, $r = .264$), indicating that the effect of test order is a real order effect and not based on initial group differences. Due to the significant order effect, analyzes for all but the lowest test frequency will be performed for each group individually.

Differences between pre-test and post-test activations were analyzed via one sample t-test. Results reveal no significant differences between measures of pre- and post-test activations for any test frequency (see Table 2.1).

Table 2.1: **Amplitude modulation test: Frequency activations.** Results of one-sample t-test (test value 0) on differences in frequency activations across test sessions. Frequencies effected by the test order effect (i.e., frequency responses differ significantly between groups) were analyzed separately for each group. Group AD1 refers to participants who performed the adaptation test first across test sessions. AD2 refers to participants who performed the adaptation test second on across test sessions.

Frequency	Test	Statistic	df	Significant	r
250 Hz	t	-.527	15	.606	.135
Group AD1					
354 Hz	t	.604	7	.565	.223
707 Hz	t	2.242	7	.060	.646
1000 Hz	t	1.356	7	.217	.456
Group AD2					
354 Hz	t	-2.203	7	.063	.640
707 Hz	t	-1.940	7	.093	.591
1000 Hz	t	-2.017	7	.084	.606

2.4. Discussion and Conclusion

The present study tested the effects of several day long notched-music listening on the processing of frequencies below and within the removed frequency band. The three main outcomes of this study are: (1) Several day long notched-music listening induced changes in cortical frequency processing. (2) The induced changes imply an increased cortical activation for a frequency of the within-notch range. (3) The induced effect was not limited to frequencies within the music notch, but was also detected for a frequency below the music notch.

2.4.1. Comparison of EEG tests

Two separate EEG tests have been performed to measure the effects of notched music listening. One test was based on adaptation release responses, the other one was based on amplitude modulation responses. Results of the adaptation test indicate that notched-music listening significantly altered the frequency processing in both notch ranges (below and within the notched frequency band). In detail, after the music listening period an increased difference between frequency responses was detected for each notch range. Further analyzes on across test sessions showed increased activations for frequencies in 1 octave distance to the edge frequency (250 Hz and 1000 Hz), but detected no changes for test frequencies in 0.5 octave distance to the edge frequency (354 Hz and 707 Hz). Results of the amplitude modulation test show increased differences between frequency responses of the below-notch range. However this effect was limited to participants who performed the Amplitude modulation test first on both test sessions (test order effect, see below). No further changes between pre- and post-test measures were detected. The two different EEG tests were performed to identify the most appropriate measure for detecting changes in cortical frequency processing. When comparing the outcome of both tests it becomes evident that the adaptation test has been a more sensitive and more robust measure relative to the amplitude modulation test. It has been more sensitive in the sense that only the adaptation test detected the smaller effect of notched-music listening for the within-notch range. And it has been more robust in a sense that the performed test order did not affect the test outcome. By virtue of the test order effect, the results of the amplitude modulation test have to be treated with caution. Due to the detected order effect each group had to be analyzed separately, and the consequently reduced sample size might have effected

the test results. It has been demonstrated that this effect was not based on initial group differences, as participant measures did not differ during the pre-test session. The differences between groups must therefore be induced by the test order in the post-test session. One possible explanation for such an order effect might be that the stimulus presentation itself affected the test outcome. In both tests stimuli consisted of frequencies below and within the music notch. The notched frequency range has therefore been stimulated throughout the first test, and this notch stimulation might have weakened the measures of notched-music listening for the second test. In line with this idea, the amplitude modulation test detected effects of notched-music listening only for participants who performed this test first. However, independent of the reasons for the detected order effect, the adaptation test has clearly outperformed the amplitude modulation test in the present study and will therefore be applied in the remaining two studies of this thesis.

2.4.2. Result 1: Induced changes in cortical frequency processing

Our first finding is in line with the research performed by Pantev and colleagues (e.g., Okamoto et al., 2010; Pantev et al, 1999; Stein et al., 2015a). Listening to notched music for several hours per day on a number of subsequent days is sufficient to alter the cortical processing of frequency information within the music notch. Pantev suggested that the induced changes are based on lateral inhibition. Neurons that are tuned to frequencies of the music notch are actively suppressed while listening to the notched music, and the continuously suppression creates over time a functional deafferentation (Pantev et al, 1999), which leads to a deactivation of the tested within-notch frequency. Such a deactivation has been reported in all studies by Pantev and colleagues, however the results of our study indicate an opposite

effect. While one test failed to detect induced changes for the within-notch range (Amplitude modulation test), the results of the other test clearly showed an increase in cortical activation for one of the within-notch frequencies (Adaptation test). The reason why the amplitude modulation test, a test which used a similar approach as the group around Pantev, failed to detect effects of notched-music listening might lie in the above mentioned limitations due to the detected test order effect. One could speculate that a larger number of participants who performed this test first or exclusively might change the outcome of this test. However, such efforts are more suited for studies that aim to replicate the test design and results reported by the group around Pantev. The aim of the present study was to investigate effects of notched-music listening and to detect an appropriate measure to do so. Additional testings have therefore been waived for the present study.

2.4.3. Result 2: Increased activation for frequency in within-notch range

Reasons for the conflicting results between the adaptation test and the findings by Pantev and colleagues might be found in the procedural differences between the performed testings. The studies by the group around Pantev were all rather similar. They all measured responses to amplitude modulated sounds via MEG, and the test frequency has always been the centre of the music notch. Responses in the present study are based on an adaptation design, were measured via EEG, and the within-notch frequencies lied below and above the notch centre. While the different imaging techniques and the different approaches to measure frequency processing might account for some variations in test outcomes, they could hardly account for opposite results. Which raises the question whether the differing relation of the tested frequencies to the notch centre could explain the result discrepancies. The current study

provides no direct measure for the frequency at the notch centre, however, the measured frequencies enclose the notch centre and allow therefore to estimate the effect for the centre frequency. The discrepant results across studies can be considered in two different ways, either as additional results, or as contradictions. The first consideration is based on the idea that notched-music listening induced reduced activations at the notch centre, as suggested by Pantev and colleagues, and that the adjoint areas, the frequencies enclosing the notch centre, consequently increased their responses. The second consideration is based on the idea that the induced changes are more linear across the notched frequency band. The increased activation detected for the 1 octave tone would therefore represent the general trend of the induced effect, including the notch centre. Considering the large number of studies that find a decreased activation at the centre frequency, the first consideration might be preferable. However, as all these studies were performed by the same group, applying identical protocols and measures, more research is needed to strongly support any of the above mentioned assumptions.

Independent of the study outcomes, it is probable that lateral inhibition can explain the generation of the induced effects. Pantev and colleagues suggest that the frequencies within the notch are inhibited via lateral inhibition, and that the inhibition strength increases over time. However, it has been shown that inhibition and excitation of cells are strongly related and that a balance between them is crucial for the functioning and the maintenance of cortical networks (see Isaacson & Scanziani, 2011). Still little is known about the mechanisms that help to establish and maintain this balance, however first results indicate that cortical networks govern the balance between excitation and inhibition self-organized (Dudek & Sutula, 2007; Vogels, Sprekeler, Zenke, Clopath & Gerstner, 2011). Following the assumption of balance,

one could argue that an ongoing and increasingly strong inhibition of specific cells within a network would trigger compensating reactions, like the reduction of the inhibition strength. A reduction in inhibition strength could be realized by, for example, a decreased firing rate of the inhibitory synapses. Over time the reduced inhibition strength for cells within the notch area would create a generally weaker inhibition, and allow therefore for increased responses when stimulated. Hypothetically both assumptions are plausible, that is, an ongoing lateral inhibition could create either reduced responses or increased responses. However both effects should be limited and guided by the general pursuit of cortical balance. The compensating reaction that counteracts an unlimited decrease of cells, would therefore also counteract an unlimited increase. Further research is needed to test these ideas. For now we can only acknowledge that similar manipulations created diverse outcomes.

2.4.4. Result 3: Increased activation for frequencies in both notch ranges

The third, and last finding of the present study is related to the frequency range below the music notch. Despite the numerous studies that have been performed on notched-music listening by the group around Pantev, little is known about effects outside the notched frequency band. Since the first study in 1999, the only frequency tested outside the music notch has been a 500 Hz tone, which was used across studies as control stimulus, independent of the applied notched frequency range within the study (e.g., Okamoto et al, 2010; Stein et al. 2015; Wunderlich et al., 2015). While an effect of notched-music listening has never been detected for this control stimulus, our study shows an effect of notched-music listening on a frequency below the music notch. In fact, the change detected for the below-notch range is similar to the one detected for the within-notch range. That is, frequencies in

1 octave distance to the edge frequency showed an increase in cortical activation after the music listening period. An effect for a frequency outside the experimental manipulation (i.e., outside the frequency range of the music notch) is a good example for the complexity of frequency processing, and the interconnectivity of the auditory cortex. To understand this result it might be necessary to introduce the concept of pitch. Pitch refers to the perceived sensation of an auditory signal, which can be ranked on a scale ranging from high to low. For pure tones pitch is related to the tone frequency. A high frequency tone, for example, is perceived as a high pitch sound, and vice versa. For complex sounds it is a bit more complicated. A complex sound consists of numerous frequencies, however the perceived sound information is combined to one single pitch. Still little is known about how pitch is processed cortically (Bendor & Wang, 2005), though two main theories have been postulated. One theory, which focus on place coding, suggests that the frequency information of a sound is encoded in the activity of differently positioned neurons, while the second theory, which focus on time coding, suggests that frequency information is encoded in firing rates and firing patterns of neurons (Patel & Balaban 2001). Although both theories competed for years, a number of findings suggest that they are not mutually exclusive, as each seems to be suited best for different sounds and frequencies (Moore, 2008c). It is important to point out, that while pure tones have been used to test the effect of notched music listening, complex sounds, that is music, have been used to induce it. This distinction is rather important, as the processing of complex sounds includes the extraction and processing of harmonies, the octave based relation between frequencies. Considering this frequency relation, one could argue that the effect of notched music listening, that is the active inhibition of the notched frequency band, might has been transmitted to harmonics of notched frequencies. Support for the idea of

a widespread, and maybe, harmonic-based inhibition can be found in a number of animal studies. It has been shown, for example, that neural inhibition is more broadly tuned than neural excitation in the auditory cortex of rats (Wu, Arbuckle, Liu, Tao & Zhang, 2008). Furthermore, widespread inhibition of neurons has been demonstrated in the auditory cortex of marmosets. Interestingly this distant inhibition was often related to harmonics of the critical frequency of the activated neurons (Wang, 2013). Additionally, multi-peak neurons, that is neurons which are tuned to more than one frequency, have been found in the auditory cortex of different mammals (e.g., Fitzpatrick, Kanwal, Butman & Suga, 1993; Rauschecker, Tian, Pons & Mishkin, 1997; Sutter & Schreiner, 1991). For some of these multi-peak neurons harmonic relations have been detected between the multiple 'tuned' frequencies (Wang, 2013). The extent of these harmonic relations, as well as the general ratio of multi-peak neurons relative to single-tuned neurons seems to vary across species (see Wang, 2013). These results, as well as the last finding of the current study, suggest that manipulations in the auditory cortex are more likely to spread than to remain narrow and locally limited. However, far more research is needed to fully understand the role of neural inhibition and excitation, as well as the relevance of harmonic activations for the processing of frequency information.

Taking together, the main focus of this study was to test the effects of notched music listening, and to identify a valid measure for cortical frequency processing. Due to the shortcomings of the amplitude modulation test in the present study, the adaptation test is clearly preferable and will be used on the remaining two studies of this thesis. The current study represents the first extensive analyses of the effects of notched-music listening on frequencies below and within the notched frequency band. It has been demonstrated that notched-music listening can induce changes in cortical processing of frequency information

already after a couple of days. The induced changes have been an increased activation for a frequency within and a frequency below the music notch. While, the increase in cortical activation represents a contrast to the findings of the studies performed by Pantev and colleagues, the found effect for the below-notch range extends existing research. The latter finding demonstrates that the effects of notched-music listening are less limited or narrow than suggested by Pantev and colleagues. More research is needed to investigate this effect in more detail, and to understand how the same experimental manipulation can lead to contrasting results across studies.

CHAPITRE 3:

Article 2 (in preparation)

Auditory frequency processing during sleep

Ramona Kaiser and Marc Schoenwiesner

3.1. Introduction

Research on sleep has a rather long history. First reports on circadian rhythms, for example, can be dated back as far as 1729 (Dement, 1998). The discovery of the K-complex in 1939 can be considered as a first evidence of auditory processing during sleep. This large, sleep-specific activation can occur spontaneously (Davis, Davis, Loomis, Harvey & Hobart, 1939), as well as in response to auditory stimulation (Loomis, Harvey, and Hobart, 1939) during non-rapid eye movement sleep (for an extensive review on the K-complex see Colrain, 2005). The latter finding clearly demonstrates that auditory information can enter the sleeping brain. Since this discovery, a number of studies aimed to demonstrate that auditory information can be received and processed during sleep. In 1961, Zung and Wilson presented pre-recorded sounds to sleeping male subjects via loudspeakers while conducting EEG recordings (Electroencephalography). The presented stimuli consisted of familiar sounds, like, trains, telephone ringing, or motorcycles, and of unfamiliar sounds, like Chinese gongs, artillery gunfire, or baby crying. The EEG recordings were analyzed by counting the number

of responses and no-responses to the presented sounds. A sound response was any change in the EEG recording that occurred together with a sound presentation and that provoked changes from a deeper to a lighter sleep stage. Results show that sound responses occurred in all sleep stages, with no significant difference in number of sound responses between familiar and unfamiliar sounds. In 1960 Oswald, Taylor and Treisman demonstrated that the sleeping brain is able to process and to discriminate between complex auditory information. The authors presented sleeping subjects with recordings of their own name as well as names of others, and found that participants were more likely to awaken to their own than any other name. A number of studies have replicated these results since (e.g., Langford, Meddis & Pearson, 1974; McDonald, Schicht, Frazier, Shallenberger & Edwards, 1975, Portas et al, 2000). Evidence that auditory information reaches the sleeping brain comes also from a rather different line of research which is focussing on dreams. A number of studies shows that auditory information is likely to be integrated in a person's dreams (Berger, 1963; Burton, Harsh & Badia, 1988; Ramsey, 1953).

An increasing number of research on auditory processing during sleep is based on the mismatch negativity (MMN). The MMN is a ‘change-specific’ auditory ERP component (Näätänen, Paavilainen, Rinne & Alho, 2007; Näätänen & Winkler, 1999) which is elicited by a rare deviant stimulus after the repeated presentation of a frequent standard stimulus (Garrido, Kilner, Stephan & Friston, 2009). The MMN represents a negative deflection around 100 - 200 ms after stimulus onset (Atienza & Cantero, 2001b), and can be elicited by changes in loudness, frequency or any other physical feature that separates the deviant stimulus from the standard stimulus (see Colrain & Campbell, 2007; see also Atienza, Cantero & Dominguez-Marin, 2002), as well as by changes of presentation patterns, like the violation

in a sequence of tones (Nordby, Roth Pfefferbaum, 1988; Sculthorpe, Ouellet & Campbell, 2009). The MMN can only be elicited if the standard signal has been presented sufficiently long or often. This repeated or prolonged presentation is necessary to create a memory trace of the auditory signal against which new incoming information is compared to (Atienza, Cantero & Dominguez-Marin, 2002). Most research on MMN during sleep is based on frequency deviations and the results are somewhat inconsistent. A number of studies show that MMN can be elicited during rapid eye movement (REM) sleep (e.g., Atienza, Cantero & Gómez, 2000; Loewy, Campbell & Bastien, 1996; Nashida et al., 2000), if the frequency difference between deviant and standard stimulus is sufficiently large (Sabri & Campbell, 2005). Results for non-REM (NREM) sleep are less coherent. While some authors argue that MMN can be elicited in stage 1, the sleep onset period, and stage 2 of NREM sleep (see Ibáñez, Martín, Hurtado & López, 2009), others argue that MMN is restricted to REM sleep and can not be elicited during NREM sleep (see Campbell & Colrain, 2002; see also Colrain & Campbell, 2007).

Besides MMN, adaptation is another, and simpler approach to measure frequency processing. Adaptation refers to the reduced cortical activity for a signal which has been presented repeatedly or over an extended period of time. This phenomenon is fairly robust and has been shown in different domains (see Grill-Spector, Henson & Martin, 2006). The reduced cortical activation for the adapter frequency can be used to measure a frequency specific response for a subsequently presented probe frequency. The probe frequency gives rise to an adaptation release response which reflects the activation of fresh, unadapted neurons. During wakefulness it has been shown that a strong frequency specific response can be elicited after long adaptation (Lanting, Briley, Sumner & Krumbholz, 2013), and for sufficient differences between adapter and probe frequencies (Butler, 1968; Briley & Krumbholz, 2013).

In the present study adaptation has been used to test whether frequency specific responses can be measured during whole night sleep. Two-tone stimuli have been presented via in-ear headphones to sleeping participants throughout one test night. Stimulus responses have been analyzed for the sleep stages NREM-2, NREM-3 and REM, as well as for wakefulness. Response differences would indicate state or sleep-stage related differences in frequency processing. To our knowledge this is the first time adaptation is used to test auditory frequency processing during sleep.

3.2. Methods

3.2.1. Participants

A total of 10 persons (5 male and 5 female), with an average age of 24 years (age range 22 – 28 years) participated as paid volunteers in the present study. All participants provided written informed consent, had normal or corrected-to-normal vision and none of the participants reported a history of hearing disorders or neurological diseases. Participants were screened for normal hearing and normal sleeping. Normal hearing (i.e., hearing thresholds below 20 dB HL) was tested with a threshold test for octave-spaced frequencies between 125 Hz and 8000 Hz. Hearing tests were performed at the International Laboratory for Brain, Music and Sound Research (BRAMS) in Montreal, Quebec/Canada. The sleep related screening consisted of psychometric questionnaires as well as actiwatch measurements of five successive days and nights before the test night. The questionnaires were applied to screen for depression (Beck depression inventory), anxiety (Beck anxiety inventory), as well as general sleep quality (Pittsburgh sleep quality index). Participants with low scores across all

questionnaires were included in this study (Beck anxiety inventory: < 21; Beck depression inventory: < 10; Pittsburgh sleep quality index: < 5). All sleep recordings were performed at the sleep laboratory at the centre for geriatric research at the University of Montreal (CRIUGM) in Montreal, Quebec/Canada. The study was in accordance with the Declaration of Helsinki and approved by the ethics committee of the Center for geriatric research at the University of Montreal (CRIUGM) in Montreal, Quebec/Canada.

3.2.2. Material

An adaptation design, similar to the adaptation test in study 1 (Kaiser & Schoenwiesner, 2017, in prep.), was used to measure auditory processing of frequency information throughout whole night sleep. A total of three stimuli were presented in this study. Each stimulus consisted of two merged pure tones, an adaptation tone and a following probe tone. The adaptation tone was, constant across stimuli, a 1000 Hz tone with a length of 500 ms, including a 10 ms cosine fade in. The probe-tone frequency varied between stimuli and ranged from 0.5 octave, 1 octave, and 1.5 octave below the adaptation tone frequency (i.e., 707 Hz, 500 Hz and 354 Hz). Each probe tone lasted 100 ms, including a 10ms cosine fade out. Both tones, adaptation tone and probe tone, were adjusted to a sound level of 40 dBA SPL, pleasant for sleep.

3.2.3. Design

The study followed a within-subject design with the three variables '*State', 'Stage'*, and '*Frequency'*. The first variable comprised two different states of wakefulness and sleep. The second variable comprised the three sleep stages, NREM-2, NREM-3 and REM. The last

variable comprised the three probe tone frequencies. The measure of interest has been the differences in auditory frequency processing within and across sleep stages and states.

3.2.4. Procedure and Data acquisition

EEG recordings were performed during one test night in one of two similar test rooms. Each test room was equipped with a single bed, a chair, and a nightstand for participants comfort, as well as an EMBLA Titanium™ system (Embla, Broomfield, USA) for EEG recordings. Participants were asked to arrive at the sleep lab in the evening, a few hours before their average sleep time. Upon arrival participants were prepared for the test night, and the recording started as soon as participants wished to go to sleep. Stimuli were presented to both ears via custom made in-ear headphones. Throughout the test night the stimuli were presented in pseudorandom order, preconditioned to alternate between probe tone frequencies without direct repetition of the same frequency, with a jittered inter stimulus interval ranging from 450 ms to 500 ms. Stimulus presentation was realized using a transportable TDT RM1 device (TDT: Tucker-Davis technologies™) together with Matlab©. Electrophysiological signals were recorded from 21 electrodes with a sampling rate of 256 Hz using Embla® RemLogic™ software. The recorded signals consisted of electroencephalography (EEG), electromyography (EMG), electrocardiography (ECG), and electrooculography (EOG). The EEG signal was recorded from 12 electrodes positioned at Fz, F3, F4, Cz, C3, C4, T7, T8, Pz, Oz and both mastoids. The ground electrode was placed at Afz, the reference electrode at Fpz. The EMG signal was recorded from the chin's centre, as well as the chin's left and right side (3 electrodes). The ECG signal was recorded bilaterally of the sternum below the clavicle (2 electrodes). The EOG signal was recorded from 2 electrodes positioned

around the eyes, laterally below the left eye, and laterally above the right eye. In the morning participants were woken at a previously agreed time. Across participants a test night lasted in average 8.2 hours (range of 7.4 hours to 9.25 hours). In average participants went to bed around 11pm (9.31 pm to 12.20 am) and were woken up at around 7 am (range: 6 am to 9.30am). Upon leaving, participants were asked to answer a sleep related questionnaire related to the test night.

3.2.5. Data processing

For each night recording sleep stages were scored by one experienced scorer (Iber, Ancoli-Israel, Quan, 2007). Subsequently each EEG recording was preprocessed using the EEGlabⓒ toolbox (Delorme & Makeig, 2004) and ERPlabⓒ toolbox (Luck & Lopez-Calderon, 2010) in combination with Matlabⓒ. The processing steps for each night recording have been as follows: (1) Sleep stage scores were assigned to the data samples of each night recording. (2) Across one night recording identical sleep stage scores were combined into one data set, resulting into four separate datasets per test night, one data set for wakefulness and one per sleep stage. (3) The signal of each dataset was re-referenced to the averaged mastoids signal and filtered applying two different basic FIR (finite impulse response) filters. First, a notch filter was used to remove a 32 Hz noise which was found in all recordings (edge frequencies: 31 Hz and 33 Hz). Subsequently bandpass filter were applied with a lower edge frequency of 1 Hz and a higher edge frequency of 30 Hz. (4) Independent component analysis (ICA) was performed to detect and remove eye blinks and eye-movement related artifacts in the EEG signal. In preparation for the ICA noisy samples and channels were manually removed from the data set. (5) Following the ICA, external electrodes (EMG, ECG and EOG)

were removed, and the continuous EEG-recording was epoched with epochs ranging from 200 ms prior probe tone onset (i.e., 300 ms after stimulus onset) to 200 ms post stimulus offset. Epochs were baseline corrected relative to the 200 ms interval prior the probe tone onset. (6) EEGlabⓒ's automatic artifact rejection for epoched data was performed with the initial threshold of 5 standard deviations and a threshold limit of 1000 microVolt. In average 4% of epochs (range: 2% to7% of epochs) were rejected by the end of the signal preprocessing, resulting in an average number of 4015 trials per stimuli for NREM-2 (range across stimuli: 4007 to 4026), 1284 trials per stimuli for NREM-3 sleep (range across stimuli: 1280 to 1286), 1343 trials per stimuli for REM sleep (range across stimuli: 1338 to 1349), and 192 trails for wakefulness (range across stimuli: 190 to 193). (7) Finally average ERPs were calculated for each sleep stage and probe tone frequency. An example of the sleep pattern of one participant is given in Figure 3.1. A region of interest (ROI) has been determined for analyzes that included all central and frontal EEG electrodes (Fz, F3, F4, Cz, C3, C4). The electrode selection is based on the frontal and central location of known N1 and P2 generators. A time window which comprised the N1 and P2 deflections was determined from averaged ERP waveforms for each probe tone. For wakefulness the time window ranged from 50 ms to 245 ms after probe tone onset. Across sleep stages the time window ranged from 77ms to 268ms after probe tone onset (see Figure 3.2 and Figure 3.3). Subsequently cortical probe tone responses were ascertain for each recording based on the area-under the curve (AUC) within the selected N1-P2 window. AUC values were calculated as root mean square across ROI channels (mean across window samples). The resulting AUC values have been used for data analyzes.

A total of four participants had to be excluded from data analyzes. One participant was excluded due to a blackout during the night. The remaining three participants had to be excluded due to poor signal quality of one or more ROI electrodes in the night recording. However, these three participants were included in one analysis for wakefulness (see below).

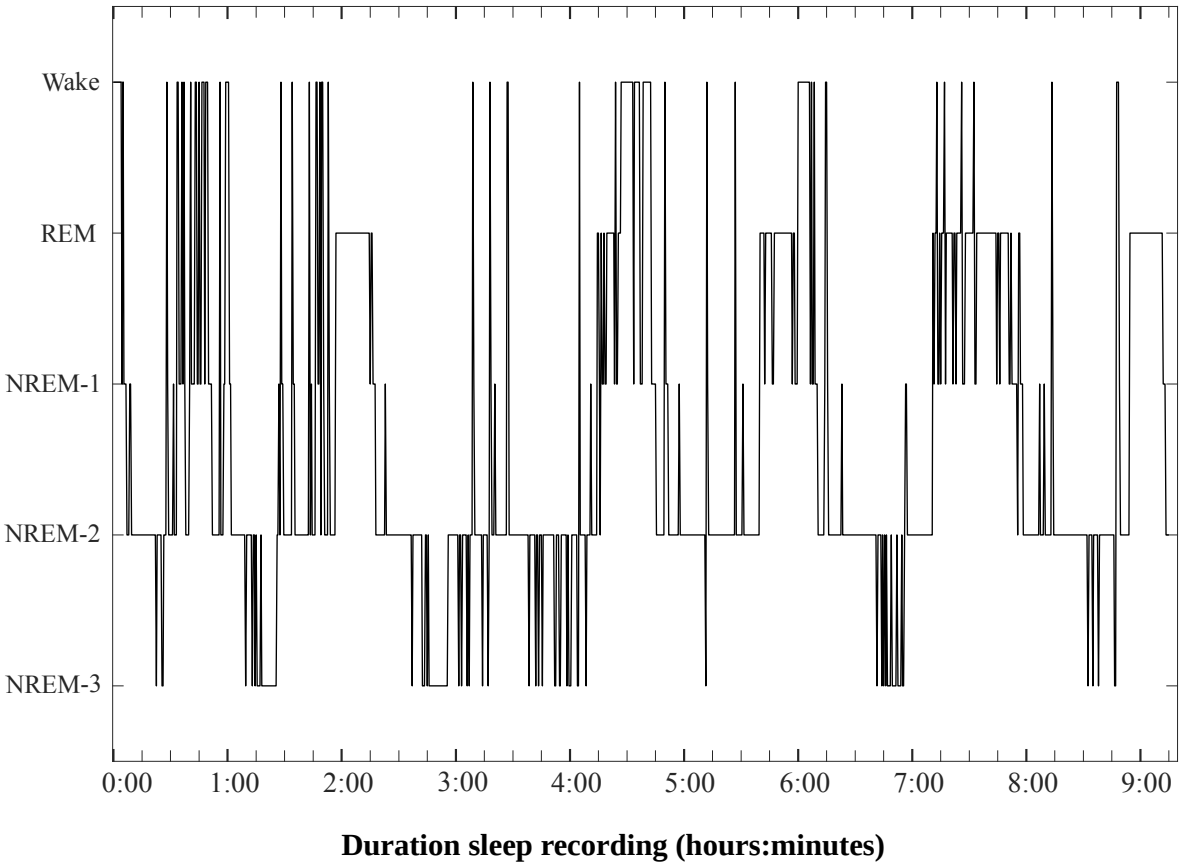


Figure 3.1: Hypnogram of one participant. Example of sleep pattern of one participant. Y-axes: Sleep stage coding including wakefulness. X-axes: Duration of sleep recording (hours:minutes)

Figure 3.2: **Grand average ERPs during sleep**. Grand average ERPs (n = 6) for probe tones during the three analyzed sleep stages (NREM-2, NREM-3, and REM). Grey shaded squares indicate the range of the N1-P2 window used to calculate the AUC values. Shaded areas indicate the standard error across participants.

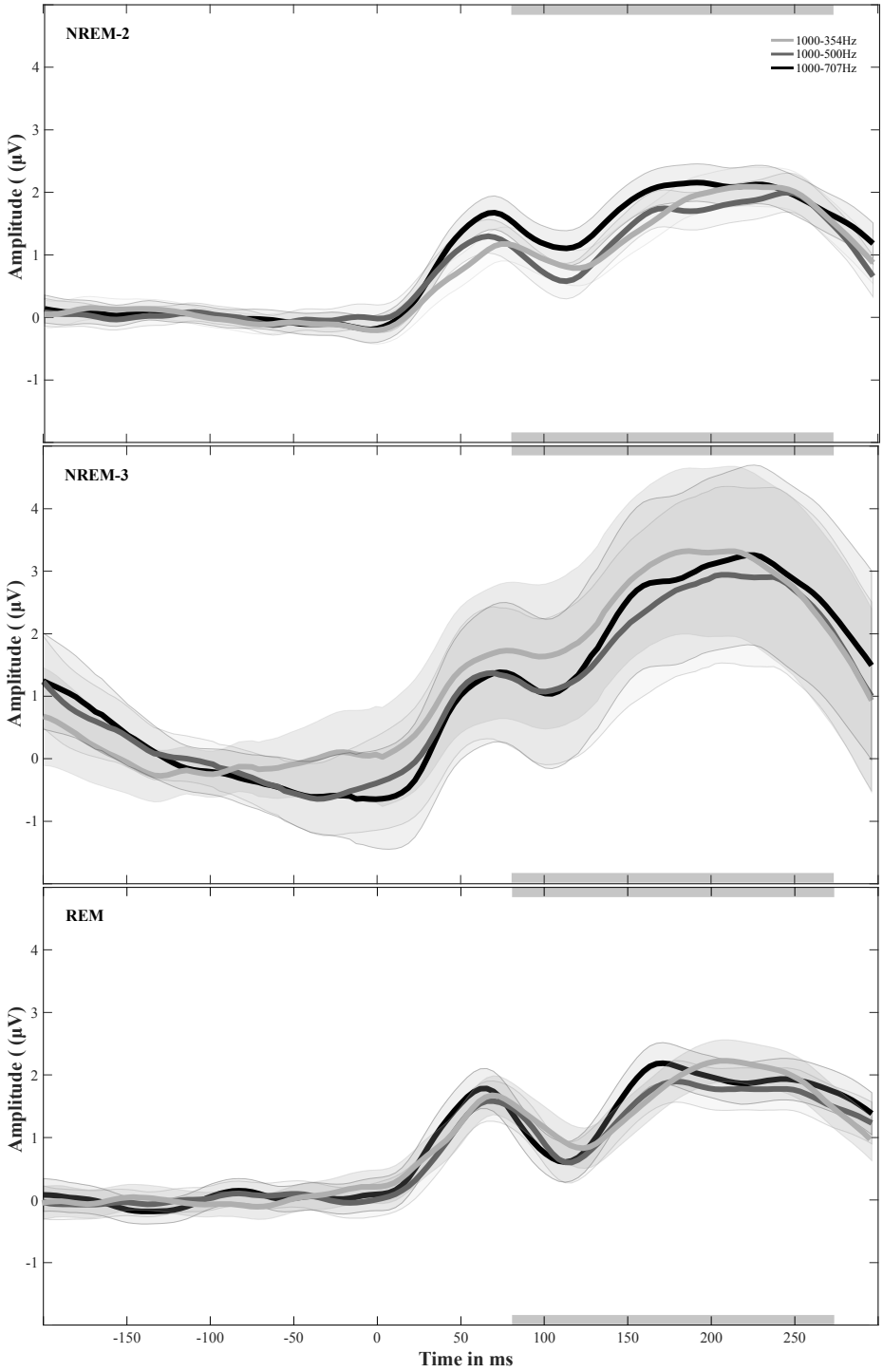
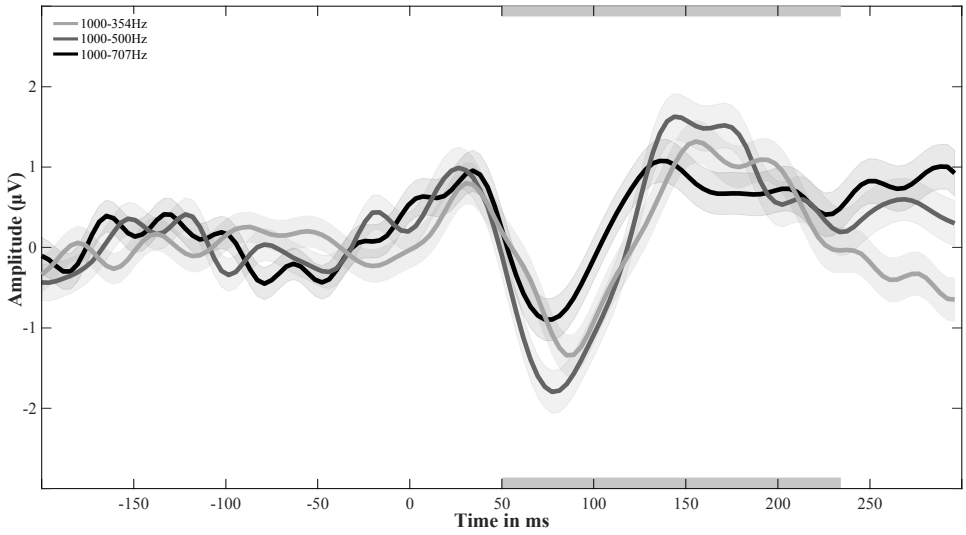


Figure 3.3: **Grand average ERPs during wakefulness**. Grand average ERPs for probe tones during wakefulness (n=6). Grey shaded squares indicate range of the N1-P2 window used to calculate the AUC values. Shaded areas indicate the standard error across participants.



3.3 Analyses and Results

The effect of sleep on auditory frequency processing has been investigated by analyzing differences in cortical activations for the presented probe tones within each sleep stage, and between wakefulness and sleep. All results reported in this sections have been adjusted for multiple comparisons (i.e., Bonferroni correction).

3.3.1. Frequency processing during wakefulness

In a first step, cortical activations during wakefulness were ascertained by comparing responses across frequencies. Analyses were performed on two sets of data. One data set comprises all participants that were tested in complete and uninterrupted night recordings (Test 1, n = 9). The second data set comprised all participants whose night recordings fit the

criteria of the ROI analyzes (Test 2, n = 6). The data sets were analyzed in two separate one-sample F-tests. Results of both tests indicate a significant difference between frequency responses (*Test 1*: $F_{(2,16)} = 5.065$, $p < .05$, $eta^2 = .388$; *Test 2*: $F_{(2,10)} = 5.829$, $p < .05$, $eta^2 = .538$). Post hoc analysis for both tests show a significant difference between the two lowest test frequencies, 354 Hz and 500 Hz, with a significant higher activation for the 500 Hz tone relative to the 354 Hz tone (*Test 1*: $t_{(8)} = -3.575$, $p < .01$, $r = .784$; *Test 2*: $t_{(5)} = -4.599$, $p < .01$, $r = .899$). The effect size r is hereby calculated as $sqrt(t^2/(t^2 + df))$, as described by Field (2009). No other significant differences between frequencies were found (see Table 3.1). These results indicate that the reduced number of participants who fulfill the ROI channel requirements is sufficient to detect differences in frequency specific responses during wakefulness.

Frequency differences	**Test**	**Statistic**	**df**	**Sign.**	**r**
Test 1 (n = 9)					
354 Hz - 500 Hz	t	-3.575	8	.007**	.784
500 Hz - 707 Hz	t	2.211	8	.058	.616
354 Hz - 707 Hz	t	-.969	8	.361	.324
Test 1 (n = 6)					
354 Hz - 500 Hz	t	-4.599	5	.006**	.899
500 Hz - 707 Hz	t	1.614	5	.168	.585
354 Hz - 707 Hz	t	-1.491	5	.196	.555

Table 3.1: **Probe tone responses during wakefulness.** Results of paired sample t-tests on response differences between the presented three probe tones during wakefulness (post hoc analyses). Significance levels of performed analyzes are indicated as follows: *** $p < .001$; ** $p < .01$; * $p < .05$.

3.3.2. Frequency processing during sleep

Differences between frequency specific responses during sleep were ascertained by a number of one-sample F-tests, one for each sleep stage (see Figure 3.4). Results show no significant differences between test frequencies in any of the three tested sleep stages (*NREM-2*: $F_{(2,10)} = .391$, $p = .686$, $eta^2 = .073$; *NREM-3*: $F_{(2,10)} = .263$, $p = .774$, $eta^2 = .050$; *REM*: $F_{(2,10)} = .999$, $p = .402$, $eta^2 = .167$).

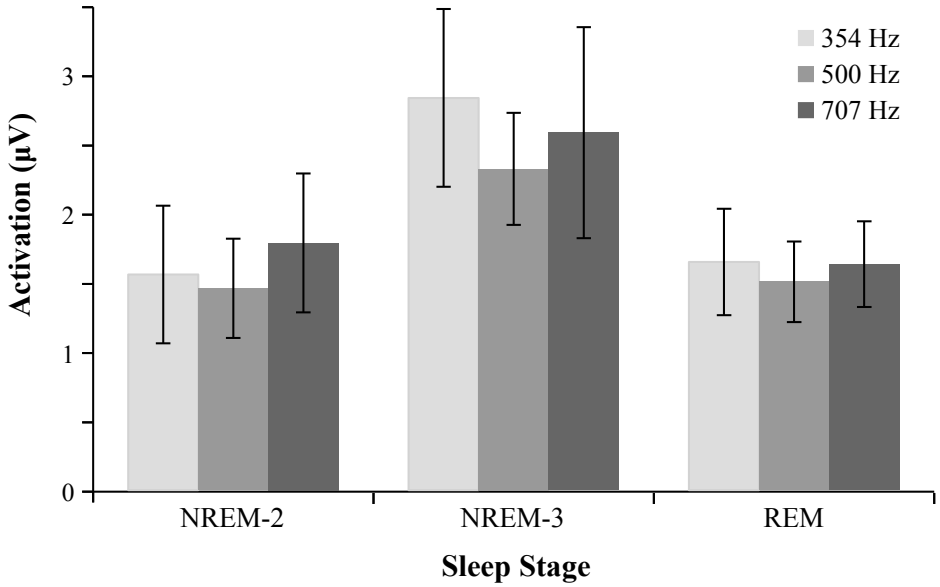


Figure 3.4: Probe tone responses during sleep. Results of one-sample F-tests on probe tone differences within each tested sleep stage. Bars represent mean activations for the presented three probe tones for each of the tested sleep stages (NREM-2, NREM-3, and REM sleep). Error bars indicate standard error across participants. No significant differences between probe tone responses were detected.

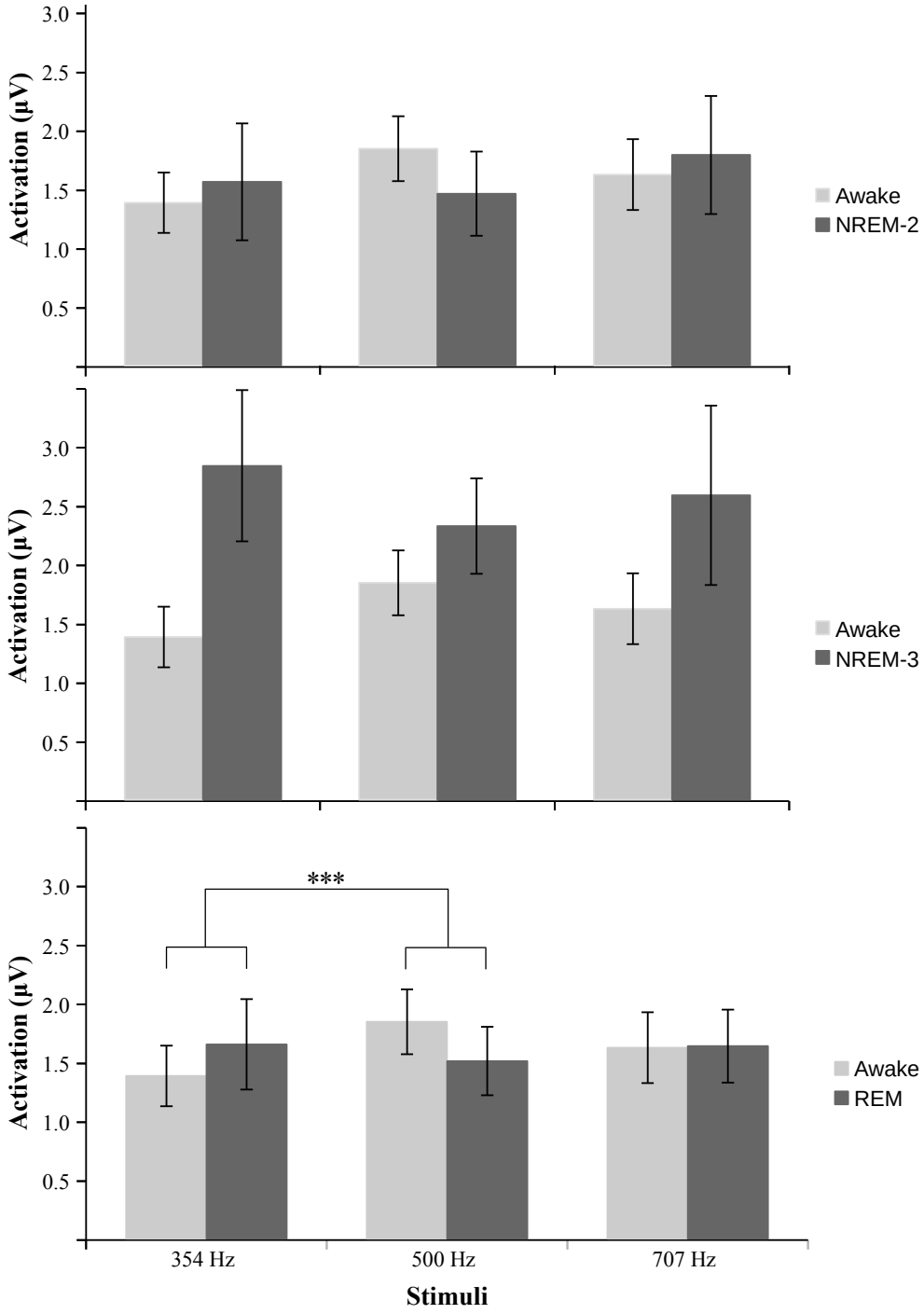
3.3.3. Differences in frequency processing between wakefulness and sleep

In a final step frequency responses during wakefulness were compared with frequency responses during each sleep stage. Separate 2 x 3 repeated measures ANOVAs were conducted with the within-subjects factors State (wakefulness and a selected sleep stage) and Frequency (the three probe tone frequencies, see Figure 3.5). Significant State x Frequency interactions were detected for REM sleep ($F_{(2,10)} = 8.441$, $p < .01$, $eta^2 = .628$). No significant main effects, or further significant interactions were found (see Table 3.2 for more results).

	Test	**Statistic**	**df**	**Error**	**Sign.**	**eta²**
NREM-2						
State	F	.001	1	5	.983	.000
Frequency	F	.682	2	10	.528	.120
State x Frequency	F	1.360	2	10	.300	.214
NREM-3						
State	F	2.429	1	5	.180	.327
Frequency	F	.003	2	10	.997	.001
State x Frequency	F	.870	2	10	.449	.148
REM						
State	F	.001	1	5	.972	.000
Frequency	F	1.345	2	10	.302	.213
State x Frequency	F	8.441	2	10	.007**	.628

Table 3.2: **Probe tone responses during sleep and wakefulness.** Results of repeated measures ANOVAs on probe tone responses across states (wakefulness and sleep). Separate ANOVAs have been performed for each sleep stage. Significance levels of performed analyzes are indicated as follows: *** $p < .001$; ** $p < .01$; *$p < .05$.

Figure 3.5: Probe tone responses during sleep and wakefulness. Mean activations of probe tones for the tested sleep stages (NREM-2, NREM-3, and REM sleep). Error bars indicate standard error across participants. Significance levels of performed post-hoc analyzes (paired sample t-tests) are indicated as follows: *** $p < .001$; ** $p < .01$; * $p < .05$.



In preparation of post-hoc analyzes differences between frequency responses were calculated for REM sleep and wakefulness. The resulting differences values were analyzed in paired t-tests. Results show significant differences between responses to the two lowest frequencies, 354 Hz and 500 Hz, during wakefulness relative to REM sleep ($t_{(5)}$ = -8.040, $p < .001$, $r = .963$). No further significant effect was detected (see Table 3.3 for more results).

Frequency differences	Test	Statistic	df	Sign.	r
Wakefulness - REM					
354 Hz - 505 Hz	t	-8.040	5	.000***	.963
505 Hz - 707 Hz	t	-1.384	5	.058	.526
354 Hz - 707 Hz	t	2.180	5	.081	.698

Table 3.3: Probe tone responses during REM sleep and wakefulness. Results of post hoc analyzes (paired sample t-tests) on response differences between REM sleep and wakefulness. Significance levels of performed analyzes are indicated as follows: *** $p < .001$; ** $p < .01$; * $p < .05$.

3.4. Discussion

The goal of the current study was to test whether frequency specific responses, based on adaptation, can be measured during whole night sleep. The main results of this study have been: (1) Frequency specific responses differed during wakefulness but not during sleep. (2) Frequency specific responses differed across states, with differing responses between wakefulness and REM sleep for the two lowest test frequencies.

3.4.1. Result 1: Frequency specific responses during wakefulness and sleep

The cortical activations measured in the current study represent adaptation release responses. Such responses are based on the activation of unadapted neurons evoked by a new signal subsequent an adaptation. Results show that activations for the two lowest test frequencies (1 and 1.5 octave below the adaptation frequency), differ significantly during wakefulness but not during sleep. This finding can be interpreted in two ways. (1) Either we failed to detect response differences, or (2) the response differences diminished during sleep. Regarding the first possibility, one could argue that sleep related brain activity, which varies greatly from brain activity during wakefulness, induced difficulties to measure cortical responses for the presented stimuli. In the current study the repetition rate per stimulus was high for each sleep stage, and averaging across stimulus repetitions (average ERPs) should reduce the impact of sleep-stage related background activity to some extent. Therefore one could argue that the signal-to-noise ratio should have been more than adequate to detect stimulus responses, and to measure related response differences. Another aspect that could have affected the sensitivity of the applied measure are sleep-related differences for the vertex potential (N1-P2), which was used to ascertain cortical responses. It has been shown that amplitude and latency of the N1 and the P2 vary across sleep stages (e.g., Bastuji & García-Larrea, 1999; Ibanez, Martin, Hurtado & Lopez, 2009). The N1 amplitude diminishes during NREM sleep, and recovers to some extend during REM sleep (see Atienza, Cantero & Escera, 2001a). The P2 amplitude increases during NREM sleep, and recovers to about half of its wakefulness value during REM sleep (Crowley & Colrain, 2004). These sleep-related changes are certainly of relevance for the applied measures. However, as pointed out above, REM

sleep represents a specific stage during which the vertex potentials should recover to partly awake-like deflections, which implies that the detection of frequency specific adaptation responses should be more likely during REM sleep than any other sleep stage. Such a dominance of REM sleep over NREM sleep has been shown for the MMN. While disagreement exists whether the MMN can be elicited during NREM sleep, most studies report that MMN can be measured during REM sleep. The missing effect for REM sleep in the current study could indicate that recovered vertex potentials are still not distinct enough to detect differences between frequency responses. In other words the possibility that the applied measure has not been sensitive enough to ascertain response differences during sleep can not be excluded.

However, as mentioned above, it is also possible that the missing response differences during sleep are based in a different functioning of adaptation during sleep relative to wakefulness. Adaptation is frequency specific. Cells that are tuned to the adapter frequency will adapt more strongly than cells that are tuned to other frequencies (Jääskeläinen et al. 2011). Sleep related changes in neural frequency selectivity would therefore affect adaptation and the related adaptation release response. Edeline, Manunta and Hennevin (2000) showed such changes for auditory thalamic cells of natural sleeping guinea pigs. During slow wave sleep (NREM-3) the tested cells showed an increased frequency selectivity, decreased receptive fields, and a generally decreased activity. However, results on auditory cortical cells, also tested during slow wave sleep, showed no sleep related changes in the size of receptive fields or changes in frequency selectivity (Edeline, Dutrieux, Manunta & Hennevin, 2001). The authors argue that such a discrepancy between thalamic and cortical neurons could lie in greater response heterogeneity for cortical cells relative to thalamic cells. A difference that has

also described between thalamic and cortical cells for the visual system (Livingstone & Hubel, 1981). Although these results indicate certain sleep-specific changes in neural frequency selectivity, more research is needed to fully understand the underlying mechanisms and their general impact for auditory information processing during sleep. Related to our results one could argue that some of these findings support the idea that adaptation is state-dependent. Higher frequency selectivity and reduced receptive field sizes, could lead to a reduced number of neurons that adapt to a signal, as well as respond to the probe tone, resulting in reduced adaptation release responses. Future research could test this idea. For now it remains unclear whether the missing differences between adaptation release responses during sleep in our study are based in a reduced sensitivity of the applied measure, or if they reflect state-dependent differences of the adaptation.

3.4.2 Result 2: Frequency specific responses across wakefulness and sleep

The second finding indicates differences in adaptation release responses between wakefulness and REM sleep for the two lowest test frequencies (1.5 and 1 octave below the adaptation frequency). When considering this outcome it is important to keep in mind that brain activity differs extensively between wakefulness, REM sleep and NREM sleep (Hobson, 2005). A direct comparison between responses recorded during wakefulness and responses recorded during any sleep state is therefore rather controversial. Any detected difference has to be treated with caution, as it could either originate from real response differences, or be caused by state-specific brain activity. On the other hand within-subject comparisons between wakefulness and each sleep stage might still feasible, as they could help to detect trends and to stimulate new research questions. The detected differences between wakefulness and REM

sleep indicate reduced differences between the two lowest test frequencies for REM sleep relative to wakefulness. The difference seems to be driven by a reduced adaptation release response for the 1 octave tone, which could indicate that adaptation is state-dependent. As hypothesized above, the reduced adaptation release response could be caused by a reduced number of adapted and activated neurons. However, as pointed out before, this interpretation is based on a controversial analyses, and should therefore be considered as a data-driven support for an interesting research question for future research.

Certain limitations should be pointed out for the current study. The first one refers to the limited number of electrodes that have been used for the sleep recordings. Certainly a larger montage would have been preferable. A larger number of electrodes would have supported a better signal to noise ratio, and would have enabled more substantial analyzes relative to the performed ROI analyzes. However the electrodes selected for the ROI analyses covered the ares of the known N1 and P2 generators, and assured therefore an accurate measure of the vertex potential. A denser electrode placement within the ROI, with electrodes placed at FCz, C1, C2, F1, and F2 would have been desirable as well, however, due to practical reasons that was not possible. In our study each electrode was attached to the head via a special paste. While this paste holds the electrodes well in place throughout the night, it also limits their density due to size of the smudge. Furthermore, a larger number of participants could have helped to strengthen the study results. However, due to the strong ‘non-effect’, found for the tested participants, additional testings were waived. Null-results rarely find their way into scientific literature, however they are of significance. The results of the present study, for example, raise new and interesting questions. The most pressing one is how adaptation is affected by the different sleep stages. An interesting approach to investigate

this question would be a design that tests adaptation release responses as well as adaptation. This could be realized by presenting probe tones in isolation as well as in combination with the adapter tone. Another interesting approach would be to vary the length of the adapter tone, which would allow to test whether adaptation builds up slower during sleep relative to wakefulness, or whether differences exists across sleep stages. These are just two of many research questions that could be extracted from the current study, and that would help to learn more about adaptation and the effects of sleep.

The present study represents, to our knowledge, the first attempt to measure frequency processing during sleep via adaptation release responses. The null-result of our study could indicate that frequency specific adaptation release responses cannot be measured during sleep. However, such a strong conclusion would be a mistake, keeping in mind that the failure to detect an effect is not the same as proving that it does not exist. The results of the current study show that measures recorded during sleep differ from measures recorded during wakefulness, the origins of these state differences however are unknown and raise a number of interesting questions for future research. As outlined in the discussion such differences could be based in state-specific sensitivity of the applied measure, or in state-dependent mechanisms of adaptation itself. Many interesting research questions have been raised by this study, which hopefully will be addressed in future research.

CHAPITRE 4:

Article 3 (in preparation)

Auditory plasticity induced during sleep

Ramona Kaiser and Marc Schoenwiesner

4.1. Introduction

Humans spend, approximately, one third of their lifetime sleeping. This tremendous amount of time might explain why throughout human history numerous ideas and theories have been postulated about the meaning and the significance of sleep (see Barbera, 2008; see also Perälä, 2014). Research on sleep has increased tremendously in the last decades, yet little is known about its function (Walker & Stickgold, 2006). It has been hypothesized that sleep aids to conserve energy, to restore brain tissue, and to detoxify the brain (see Maquet, 2001). It has also been hypothesized that rapid eye movement (REM) sleep could play an important role in maintaining the proficiency of cortical networks (Crick & Mitchison, 1983). In 2013 Xie and colleagues provided first evidence of a clearance function of sleep. The authors showed that injected tracers are removed faster from the brain of sleeping mice relative to mice that were awake. The improved 'cleaning' proficiency has been related to an increased extracellular space, and therefore an increased flow of cerebrospinal fluid in the sleeping brain relative to wakefulness. A number of studies indicate that sleep can enhance learning and memory (for a review see Diekelmann & Born, 2010), the underlying

mechanisms however remain still unclear. In the following the term ‘learning’ will be used in a broader sense, including conditioning, performance improvements, changes in sensory perception, as well as cortical changes due to an interaction with or exposure to a training paradigm. Existing research on sleep and learning can be divided into three approaches, each with a slightly different focus on sleep relative to the training and testing period. In the first approach the effect of sleep on learning is measured indirectly. Training effects are tested during wakefulness for participants who slept or napped after the training. The second approach focus on training effects in post-training sleep, and the third approach focus on training effects induced while sleeping.

Research on the first approach can be dated back as far as 1924 when Jenkins and Dallenbach demonstrated that sleep after training enhances the memory for learned material. A number of studies replicated this finding and showed a positive effect of sleep for motor learning tasks (e.g., Walker, Brakefield, Morgan, Hobson & Stickgold, 2002; Kuriyama, Stickgold & Walker, 2004), and perceptual tasks like visual discrimination (e.g., Karni, Tanne, Rubenstein, Askenasy & Sagi, 1994) or auditory memory (e.g., Gaab, Paetzold, Becker, Walker & Schlaug, 2004).

Research for the second approach aims to indicate the role of sleep in the learning process by correlating performance improvements upon awakening with deviations of sleep stage characteristics, or by detecting traces of memory consolidation during post-training sleep. Such traces could be cortical activations related to the analysis, reactivation, or incorporation of the learned material (Maquet, 2001). Results concerning sleep stage characteristics are complex. Some studies report an increase in REM sleep after training (e.g., De Koninck, Lorrain, Christ, Proulx & Coulombe, 1989), others emphasize the

importance of non-REM (NREM) sleep (Robertson, Pascual-Leone & Press, 2004), or show no effect of training on the tested sleep stages (Meienberg, 1977). It has been argued that the diversity of research outcomes is based on the characteristics of the tested task, like its nature, difficulty, or relevance (Walker & Stickgold, 2006). An interesting finding concerning memory consolidation comes from Maquet and colleagues (2000) who could demonstrate an increased brain activity in post-training sleep with activation patterns similar to those recorded during training in wakefulness.

Far less is known about the possibility to acquire new information during sleep, the last of the three presented approaches. Research on this more 'active' role of sleep in the learning process might have been hindered by the long held view that the sleeping brain is disconnected from environmental information (e.g., Steriade, 1994). However a small number of studies could demonstrate that conditioning of behaviour, and the acquiring of new memory is possible during sleep. Already in 1965 Beh and Barratt demonstrated that the response to auditory stimuli can be altered via conditioning during sleep. Based on the idea that only meaningful information is processed by the sleeping brain, the authors presented neutral sounds paired with short electrical shocks to alter the subjective meaning of the sound information. The pain-sound stimulation was performed during wakefulness (experiment 1) and sleep (experiment 2). In both experiments a change in cortical activation for conditioned stimuli could be detected. These results were interpreted as an indication that conditioning, and therefore learning, is not limited to wakefulness but can also occur during sleep. Fifer et al (2010) tested the ability of young infants to learn during sleep. The authors applied a conditioning paradigm that consisted of tones and air puffs directed at the closed eye of the sleeping newborn. Results showed an increase in conditioned responses (eye movements) for

the experimental group relative to the control group, as well as changes in cortical activation, which indicates that several hours old infants can be conditioned to sounds during sleeping. In 2012 Arzi and colleagues demonstrated that a sniffing reaction to certain tones can be induced during sleeping, and that this conditioned response has been transferred into wakefulness. Recently Andrillon, Pressnitzer, Léger, and Kouider (2017) demonstrated auditory perceptual learning during sleep. The authors showed an improvement in noise detection during wakefulness for participants who have been exposed to novel noise stimuli throughout whole night sleep. The authors interpret their results as an indication that new information can be learned while sleeping.

The current study aims to test whether it is possible to induce changes in cortical frequency processing based on auditory stimulation during whole night sleep. A number of studies have demonstrated that listening to notched music, that is music from which certain frequencies have been removed, can alter the cortical processing of the removed frequencies (e.g., Kaiser & Schoenwiesner, 2017, in prep.; Okamoto, Stracke, Stoll, & Pantev, 2010; Pantev, Wollbrink, Roberts, Engelien & Lütkenhöner, 1999). Furthermore it has been suggested that the changes, induced by notched music listening, occur rapidly and can be detected already after several hours of notched music listening (e.g., Pantev et al., 1999). The current study tests whether such changes can also be induced during whole night sleep. Following the design of study 1 (Kaiser & Schoenwiesner, 2017, in prep.) participants were exposed to notched noise during a training period, and the cortical processing of frequencies within and below the noise notch was tested before and after the noise-exposure period (pre- and post-test). In contrast to study 1, notched pink noise was used in the present study. Relative to music, pink noise allows a more controlled and more calibrated stimulation across

frequencies, as the power of the noise frequencies has been adjusted to achieve an equal amount of noise energy across octaves (Moore, 2008a). Furthermore, the training period in the present study represents a continuous passive sound exposure throughout one night of sleep, in contrast to study 1 where notched music listening has been distributed over several subsequent days. If the frequency information of the notched noise is received and processed during sleep, we expect an induced change in frequency processing after the training period, similar to the results found for notched music listening during wakefulness.

4.2. Methods

The present study consisted of three EEG-recordings: One night recording, performed throughout whole night sleep (modulation night), and two test recordings, performed during wakefulness directly before and after the modulation night (pre-test and post-test). The night recording was performed to extract information about participants sleep quality and composition (i.e., sleep stage information). The test recordings were performed to measure the effect of whole night notched-noise exposure.

4.2.1. Participants

A total of 10 persons (5 male and 5 female), with an average age of 23.7 years (age range 21 – 27 years), provided written informed consent and participated as paid volunteers in the present study. Participants were screened for normal hearing and sleep. Normal hearing (i.e., hearing thresholds below 20 dB HL) was tested via a threshold test for octave-spaced frequencies between 125 Hz and 8000 Hz. The sleep related screening consisted

of psychometric questionnaires and actiwatch measurements. Actiwatch measures were performed during the 5 successive days and nights before the test night. The psychometric questionnaires consisted of the Beck depression inventory (BDI), the Beck anxiety inventory (BAI), as well as the Pittsburgh sleep quality index (PSQI). Participants with low test scores were included in this study (BAI: < 21; BDI: < 10; PSQI: < 5). All participants had normal hearing, normal or corrected-to-normal vision, and no reported history of hearing disorders or neurological diseases. The study was in accordance with the Declaration of Helsinki and approved by the ethics committee of the Center for geriatric research at the University of Montreal (CRIUGM) in Montreal, Quebec/Canada. Hearing tests were performed at the International Laboratory for Brain, Music and Sound Research (BRAMS) in Montreal, Quebec/Canada, all remaining testing was performed at the sleep laboratory of the CRIUGM.

4.2.2. Stimuli and Materials

4.2.2.1. Night recording

The signal presented throughout the night recording consisted of notched pink noise. The cutoff frequencies of the applied notch filter were 600 Hz and 1200 Hz. The notched pink noise was presented with 40 dBA SPL. The notched pink noise was created in Matlab© in combination with a transportable Tucker-Davis technologies™ RM1 device, and presented continuously throughout the night.

4.2.2.2. Test recordings

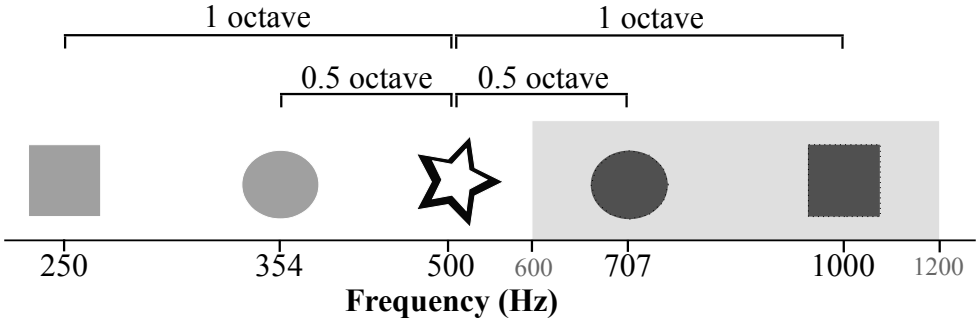
The stimuli used in this study are identical to the stimuli presented in the adaptation test of study 1 (notch music study performed during wakefulness). Each stimulus consisted of two merged pure tones, an adaptation tone which was followed by a probe tone. The adaptation tone was a 500 Hz tone with a length of 500 ms, including a 10 ms cosine fade in. The probe tone frequency differed across sound stimuli and comprised the four test frequencies (250 Hz, 354 Hz, 707 Hz, and 1000 Hz). Each probe tone had a length of 100ms, including a 10ms cosine fade out. Following the design of study 1, the selection of the adaptation and probe tone frequencies were based on the following criteria: (1) The adaptation tone frequency lies below the lower cut-off frequency of the notched noise (600 Hz) and outside its critical bandwidth. The critical bandwidth was calculated based on equivalent rectangular bandwidth (ERB) method:

$$\mathbf{ERBN = 24.7(4.37 * frequency + 1)}$$

(Moore, 2008b)

The lower cut-off frequency was estimated around 510 Hz, and the filter edge frequency was set to 500 Hz. (2) Probe tone frequencies lie 0.5 octave and 1 octave below, and above the adaptation tone frequency. (3) Half of the probe tone frequencies lie below, and the remaining half lie within the frequency range of the notched noise (see Figure 4.1). The sound level of both stimulus tones, adaptation tone and probe tone, was adjusted to 80 dBA SPL.

Figure 4.1: **Graphical display of frequency composition.** Display adopted from study 1 (Kaiser & Schoenwiesner, 2017, in prep). Grey shaded area represents the frequency range of the applied noise notch. The upper and lower cut-off frequency of the notch filter are shown as grey numbers. The edge frequency, represented as a star, lies more than one critical bandwidth below the lower cut-off frequency of the noise notch. The test frequencies are shown as squares (test frequencies in 1 octave distance to the edge frequency) and circles (test frequencies in 0.5 octave distance to the edge frequency). Test frequencies within the frequency range of the noise notch are displayed in darker grey, test frequencies below the noise notch are displayed in lighter grey.



4.2.3. Design

The test recordings followed a within subject design with three variables: '*Test session',* comprising the EEG recordings performed before and after the modulation night, '*Test frequencies',* comprising the four probe tone frequencies, and '*Notch range*', comprising test frequencies below and within the frequency range of the notch (below and within the notch). The effect of notched-noise exposure was quantified by comparing differences between pre- and post-test measures for notch range activations and test frequencies.

4.2.4. Procedure and Data acquisition

EEG recordings were performed in one of two test rooms, each equipped with a single bed, a chair, and a nightstand for participants comfort. Participants were asked to arrive at the

sleep lab in the evening, a few hours before their average sleep time. Upon arrival participants were prepared for the night and test recordings. In the morning participants were woken at a previously upon agreed time, and prepared for the second test session. These preparations included, ensuring that participant are fully awake, and replacing electrodes if necessary. After the post-test participants were asked to answer a questionnaire related to the sleep during the modulation night. The recorded signal during the night and the test recordings comprised electroencephalography (EEG), electromyography (EMG), electrocardiography (ECG), and electrooculography (EOG), and was measured from 21 electrodes. The twelve EEG electrodes were positioned at Fz, F3, F4, Cz, C3, C4, T7, T8, Pz, Oz, and both mastoids. The ground electrode was placed at Afz, and the reference electrode at Fpz. The three EMG electrodes were placed at and bilaterally to the chin centre. The two ECG electrodes were placed below the clavicle, bilateral the sternum. The two EOG electrodes were positioned around the eyes, diagonally approximately 2 cm left and below the left eye, and approximately 2 cm right and above the right eye. The signal was recorded via an EMBLA Titanium™ system (Embla, Broomfield, USA) in combination with REM-Logic© software at a sample rate of 256 Hz. The auditory stimuli were presented to both ears via custom made in-ear headphones during the night recording and both test recordings. The presentation of the auditory signals, notched noise during the modulation night, and test stimuli during the test recordings, was realized using a transportable Tucker-Davis technologies™ RM1 device in combination with Matlab©.

4.2.4.1. Night recording

The sleep recording, including the presentation of the notched noise, started as soon as participants wanted to sleep, and ended as soon as the participant were woken up in the morning. To prevent headphones from moving or from falling out throughout the night, the in-ear headphones were attached to the participant's ears via medical tape.

4.2.4.2. Test recordings

During the test recordings participants were awake and had no task but to remain relaxed and to avoid any unnecessary head- or body movements while watching a muted and subtitled movie of their choice (passive EEG recordings). Participants were seated comfortably at the bed in about 80 cm distance to a macintosh laptop used for movie presentation (LCD screen with a resolution of 1400 x 1050 pixels). Stimuli presentation was pseudo-randomized, pre-conditioned to alternate between test frequencies below and within the frequency range of the noise-notch. Stimuli were presented with a jittered inter stimulus interval ranging from 450 ms to 500 ms. Throughout one test recording each stimulus was repeated 550 times (total of 2200 trials). One test session lasted 39 minutes.

4.2.5. Data processing

4.2.5.1. Night recording

Each sleep recording was rated by one experienced scorer to determine sleep stages. Each sleep stage scoring was hereby based on a 30 s window of the night recording (Iber,

Ancoli-Israel, Quan, 2007). The resulting sleep stage information was used to evaluate the sleep quality and the exposure to the notched noise.

4.2.5.2. Test recordings

The recorded signal was preprocessed using the EEGlabⓒ toolbox (Delorme & Makeig, 2004) and ERPlabⓒ toolbox (Luck & Lopez-Calderon, 2010) in combination with Matlabⓒ. The signal was re-referenced to the averaged mastoids activation, and filtered applying basic FIR (finite impulse response) filter. First a notch filter was applied to remove a 32 Hz noise which was detected in all recordings performed in the sleep lab. The edge frequencies of the applied notch filter were set to 31 Hz and 33 Hz. Subsequently bandpass filters were applied, a high-pass filter with an edge frequency of 1 Hz, and a low-pass filter with an edge frequency of 30 Hz. An independent component analysis (ICA) runica algorithm was performed to detect and remove blinks and eye-movement related artifacts in the EEG signal (Jung et al., 2000; Bell & Sejnowski, 1995). In preparation for the ICA, noisy data samples and channels were manually removed from each data set. Following the ICA, external electrodes were removed, and the continuous EEG-recording was epoched with epochs ranging from 200 ms prior probe tone onset (i.e., 300 ms after stimulus onset) to 200 ms post stimulus offset. The 200 ms interval prior the probe tone onset was used for baseline correction. The epoched signal was further processed applying EEGlabⓒ's automatic artifact rejection for epoched data with the initial threshold of 5 standard deviations and a threshold limit of 1000 microVolt. In average 2% of epochs (range: 0.8% to 3% of epochs) were rejected by the end of the signal preprocessing, resulting in an average number of 415 trials per stimulus during pre- and post-test recordings.

In preparation for data analyses a region of interest (ROI) has been determined that included all central and frontal EEG electrodes (Fz, F3, F4, Cz, C3, C4). Only these six electrodes will be used in the following processing steps and analyses. One participant had to be excluded from the ROI analysis due to poor signal quality in some of the required ROI electrodes during the post-test recording, another participant had to be removed due to a nearly non-existing N1 during the test recordings. (i.e., the data of eight participants will be used for analyzes). Average event related potentials (ERPs) were calculated for each participant and probe tone frequency. A time window was determined which comprised the N1-P2 deflection of the grand average responses for each test session and test frequency. The applied time window ranged from 50 ms to 265 ms after probe tone onset, (see Figure 4.2). The cortical probe tone responses were ascertained as area-under the curve value (AUC) which represents the root mean squared activation across channels within the N1-P2 window (i.e., mean across window samples). Each participants AUC values were z-score normalized across test sessions and stimuli, and the resulting normalized AUC values will be used for analyzes.

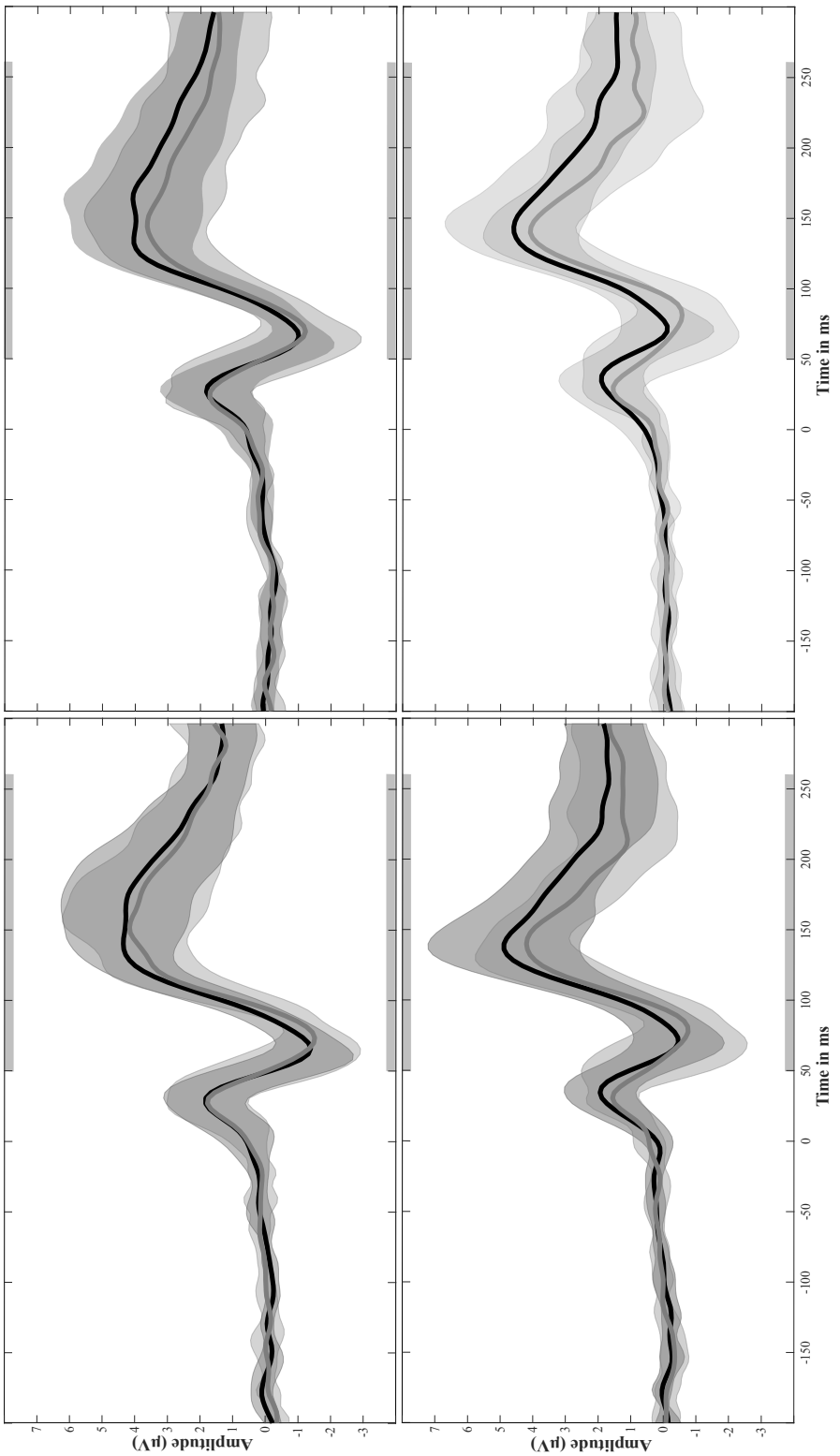


Figure 4.2: Grand average ERPs. Grand average ERPs for probe tones presented during the pre- and post-test. Grey shaded squares indicate the range of the N1-P2 window used to calculate the AUC values. Shaded areas indicate the standard error across participants. Pre-test results are shown in light grey, post-test results are shown in dark grey. *Upper left*: Response for the 250 Hz tone. *Upper right*: Response for the 354 Hz tone. *Lower left*: Response for the 707 Hz tone. *Lower right*: Response for the 1000 Hz tone.

4.3. Analyses and Results

The effect of notched-noise exposure is tested following the analysis of study 1 in this thesis. Differences in cortical activations between pre-test and post-test recordings were analyzed for both notch ranges, below and the within the frequency range of the noise notch (notch range activations), as well as for each test frequency (frequency activations). As mentioned earlier, two participants have been excluded from data analyzes. One due to a poor signal quality in one of the ROI electrodes, the other one due to a weak, nearly non-existing N1 during the test recordings. Analyzes are performed on the data of the remaining eight participants. All results reported in this sections have been adjusted for multiple comparisons (i.e., Bonferroni correction).

4.3.1. Night recording

Analyzes of the night recordings indicated that, in average, participants were exposed for 7.4 hours to notched noise while sleeping (range 6.1 hours to 8.6 hours). Per night, participants spend in average 1.3 hours in *REM* sleep (range 0.7 hours to 1.8 hours), and 6.2 hours in *NREM* sleep (range 5.4 hours to 7 hours). The average composition of NREM sleep has been as follows, 0.5 hours *NREM-1* (range: 0.3 hours to 0.8 hours), 4.3 hours *NREM-2* (range 3.6 hours to 5.3 hours), and 1.3 hours *NREM-3* (range: 0.7 hours to 2.5 hours). These data indicate that participants' sleeping behaviour can be considered as normal.

4.3.2. Test recordings

4.3.2.1 Notch range activations

In a first step activations were calculated for each notch range and each test session. Two notch range activation measures have been calculated: (1) differences between frequency responses within one notch range (Notch frequency difference), a measure that has also been used in study 1, and (2) the mean activation across frequency responses within each notch range (Notch frequency mean). To estimate changes in notch range activations across test sessions, post-test values were subtracted from the related pre-test values for both measures. The resulting values have been used in the following analyzes.

4.3.2.1a Notch range difference

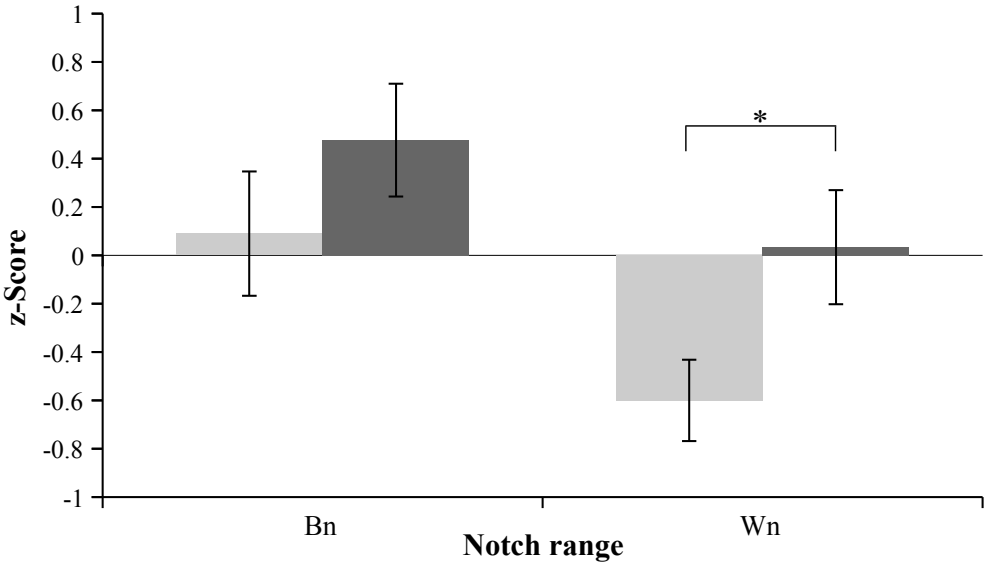
The distribution of the Notch range difference (NR-d) for both notch ranges, below and within the noise notch, were tested for normality applying Shapiro-Wilk tests. Results indicate no violation of the normally assumption for both distributions, permitting the use of parametric analyzes (*below-notch*: $W_{(8)} = .930$, $p = .516$; *within-notch*: $W_{(8)} = .965$, $p = .858$). One-sample t-test were used to test for differences in notch range activations across test sessions (see Figure 4.3). Results show no significant difference between pre- and post-test measures for any of the two notch ranges, indication that the ratio of the frequency responses within one notch range did not change across test sessions (*below-notch*: $t_{(7)} = 2.031$, $p = .082$, $r = .609$; *within-notch*: $t_{(7)} = .523$, $p = .617$, $r = .194$), with r representing a measure of effect size which is calculated as $\text{sqrt}(t^2/(t^2 + df))$, as described by Field (2009).

4.3.2.1b Notch range mean

Visual inspection of the current data, suggested a second measure to analyze mean notch range (Nr-m) activations across test sessions. The NR-m distributions for both notch ranges were first tested for normality. Results of Shapiro-Wilk tests indicate a normal distribution for each notch range (*below-notch*: $W_{(8)} = .935$, $p = .559$; *within-notch*: $W_{(8)} = .873$, $p = .160$). The differences between pre- and post-test responses were tested via one-sample t-tests (see Figure 4.3). Results show a significant difference between pre- and post-test for the within notch range ($t_{(7)} = -3.462$, $p < .05$, $r = .795$). No significant effect of test session was found for the notch range below the noise notch ($t_{(7)} = -.713$, $p = .499$, $r = .260$).

To enable a comparison between the current study and study 1 (notched music listening during wakefulness), the same analysis was performed with the adaptation test data of study 1. The NF-m values for study 1 were calculated in the same manner as described above. Tests for normality (Shapiro-Wilk tests) revealed that the resulting values were distributed normally (*below-notch*: $W_{(15)} = .969$, $p = .848$; *within-notch*: $W_{(15)} = .965$, $p = .773$). Results of one-sample t-tests on the effect of notched music listening during wakefulness revealed no significant differences between pre- and post-test measures of NF-m for study 1 (*below-notch*: $t_{(14)} = -1.553$, $p = .143$, $r = 383$; *within-notch*: $t_{(14)} = -1.824$, $p = .438$).

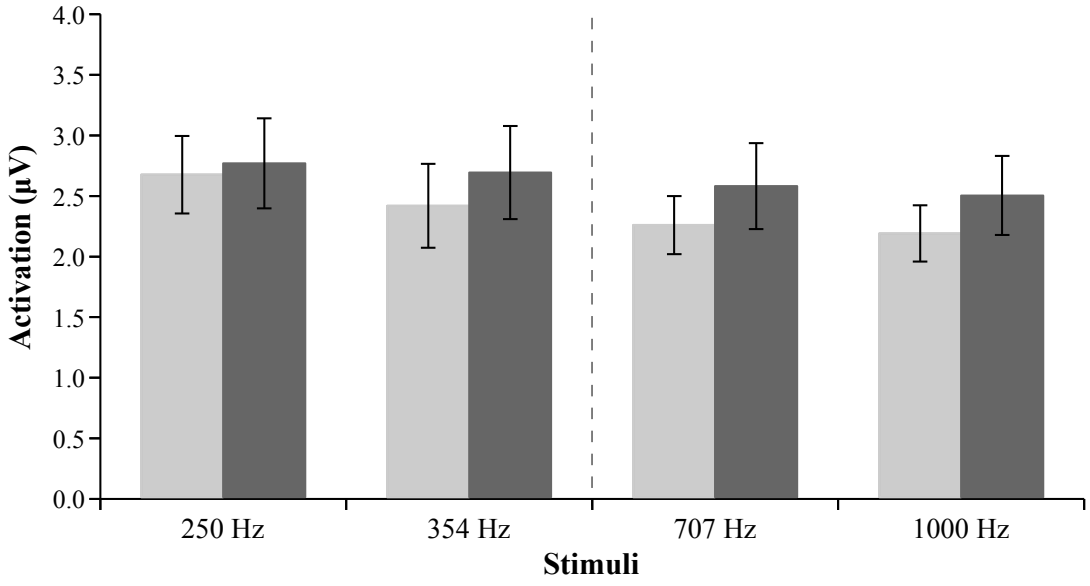
Figure 4.3: **Mean notch range activations across test sessions.** Mean notch range activations represent the mean across frequencies of each notch range per test session (Bn: below-notch; Wn: within-notch). Pre-test values are shown in light grey, post-test values in darker grey. Error bars indicate standard error across participants. Significance levels of performed analyzes (one-sample t-test: Mean notch range activation across test sessions) are indicated as follows: *** p < .001; ** p < .01; * p < .05.

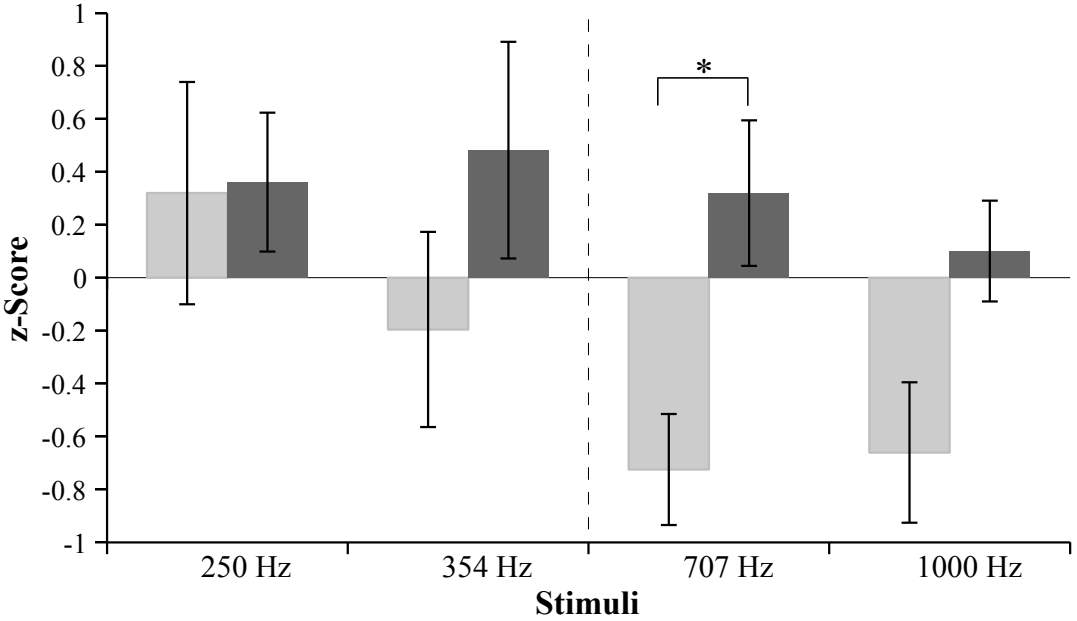


4.3.2.2. Frequency activations

Subsequent analyzes were performed for the probe tone frequencies. Differences in frequency responses across test sessions were calculated for each frequency by subtracting post-test activations from pre-test activations. The resulting values were used for analyzes. First, Shapiro-Wilk tests were performed to test for violations of the normality assumption. The distributions for each frequency was in line with this assumption, permitting the use of parametric tests (*250Hz*: $W_{(8)}$ = .872, p = .159; *354Hz*: $W_{(8)}$ = .892, p = .243; *707Hz*: $W_{(8)}$ = .913, p = .372; *1000Hz*: $W_{(8)}$ = .910, p = .355). Following, one sample t-tests were performed to test for differences in frequency activations across test sessions (see Figure 4.4).

Figure 4.4: **Frequency activations.** Frequency responses across test sessions. Pre-test values are shown in light grey, post-test values are shown in darker grey. Frequencies left of the dotted line lie below the noise notch, frequencies right of the dotted line lie within the noise notch. *Upper plot* shows mean frequency responses before z-score transform. *Lower plot* shows z-normalized data (data used for analyzes). Error bars indicate standard error across participants. Significance levels of performed analyzes (one-sample t-test: Frequency activations across test sessions) are indicated as follows: *** p < .001; ** p < .01; * p < .05.





Results show a significant difference for the lowest within notch frequency (*707Hz*: $t_{(7)} = -2.766$, $p < .05$, $r = .723$). No significant differences were found for any of the remaining test frequencies (*250Hz*: $t_{(7)} = -.089$, $p = .931$, $r = .034$; *354Hz*: $t_{(7)} = -1.156$, $p = .286$, $r = .400$; *1000Hz*: $t_{(7)} = -2.032$, $p = .082$, $r = .609$).

4.4. Discussion and Conclusion

The goal of this last study was to test whether auditory plasticity in form of changes in cortical frequency processing can be induced via notched-noise exposure during one night of sleep. The main findings of this study are, that (1) one night of notched-noise exposure is sufficient to induce detectable changes in cortical frequency processing. (2) The induced changes consisted of an increased overall activation for the within-notch range. (3) The induced effects were limited to the within-notch range, with a significant increase in frequency processing for the lowest within-notch frequency.

4.4.1. Result 1: Rapidly induced effect of notched-noise exposure

In 1999 Pantev et al. conducted the first study on notched music listening. Normal hearing participants listened to notch music for three hours per day on three subsequent days. MEG recordings were performed each day before and after the notched music listening. Changes in cortical frequency processing were detected already after the second day, which led to the conclusion that the induced effect built up rather rapidly. Similar results were reported in two more recent studies. Stein et al. (2015a, 2015b) presented, following the design by Pantev et al. (1999), notched music for three hours per day on three subsequent

days, and performed two MEG testings before and after the music listening period. Participants in both studies by Stein et al. consisted of patients who perceive auditory phantom sensations (i.e., tinnitus). In both studies significant changes in cortical processing were detected after the third day, that is after a total of 9 hours of notched music listening during wakefulness. In the present study, significant changes in cortical frequency processing were detected after an average of 7.4 hours of sleep. This result is in line with the above mentioned studies, indicating that several hours of notched signal exposure is sufficient to induce detectable changes in frequency processing. However, the present study is the first to demonstrate that cortical changes can be induced in a similar short period during sleep. Furthermore our results indicate that frequency processing remains rather precise and effective during sleep. The notch range of the sound signal could be detected (precision), and the lack of the frequency information was strong enough to induce changes for the missing frequencies (efficiency).

Existing research shows that auditory information can be perceived and processed during sleep (e.g. Oswald, Taylor & Treisman, 1960; Portas et al, 2000; Zung & Wilson, 1961), and indicates that information processing might differ across sleep stages. Results on mismatch negativity (MMN), for example, provides strong evidence for information processing during REM sleep (e.g., Atienza, Cantero & Gómez, 2000; Loewy, Campbell & Bastien, 1996; Nashida et al., 2000), but created less coherent results for NREM sleep. While some studies failed to detect MMN during NREM sleep, others limit its elicitation to certain NREM stages, like, for example, NREM-2 (see Colrain & Campbell, 2007; see also Ibáñez, Martín, Hurtado & López, 2009). Independent of these diverse results for the MMN, evidence for information processing during NREM sleep exist in the finding that

K-complexes, a sleep specific potential which is strongly related to NREM sleep, can be evoked in response to external stimulation (Loomis, Harvey & Hobart, 1939). To which extend this general prove of information processing during sleep holds for different types of information still needs to be discovered. Related to the present study, it remains unclear whether the buildup of the induced effect is limited to periods of REM sleep, or whether periods of NREM sleep have also been involved. Participants spend in average 1.3 hours in REM sleep. In case only REM sleep would have been involved in the buildup of the effect, sleep would outperform wakefulness in the efficiency to induce cortical changes. As such a dominance for sleep over wakefulness seems rather unlikely, it might be more probable that the missing frequency information of the notched noise has been 'available' throughout the night. A number of studies indicate the importance of REM and NREM sleep for learning. Relation could be detected between performance improvements and sleep stage durations, as well as between performance deteriorations and sleep deprivations (for a review see Walker & Stickgold, 2006). Further evidence for the assumption that learning is not limited to REM sleep alone comes from an interesting study by Andrillon, Pressnitzer, Léger, and Kouider (2017), who could demonstrate that auditory perceptual learning occurs throughout the night during REM sleep and NREM sleep. Interestingly the involvement of NREM sleep in the learning process seems to be rather diverse. While learning was supported during light NREM sleep (NREM-2), no learning occurred during deep NREM-sleep (NREM-3). Furthermore the authors suggested that the learning suppression during NREM-3 remains 'active' upon awakening, as material that was presented during NREM-3 sleep was reportedly not learned during post-sleep sessions. Whether these findings could also explain the effects found for notched-noise exposure in the current study remains a question for future research.

Another interesting aspect, that should be addressed in future research, is the impact of the applied sound signal for the induced notch-effect. In all studies performed during wakefulness music was used to induce the notch effect. In the current study however pink noise has been applied. As mentioned earlier, pink noise allows a controlled and calibrated stimulation across frequencies. Music contains typically less energy in higher frequencies (Stein 2015b). The spectrum related differences between music and pink noise, might translate into differently strong notched signals. It is possible that the use of pink noise enhances the effect of the notch, as all but the removed frequencies are stimulated. On the other hand, considering the frequency range of the applied notch, differences between music and pink noise might be negligible, as the notch in the current study covers a rather low frequency range (600 Hz - 1200 Hz), and the limitations of music are related to higher frequencies. An ideal way to test the assumption, that the applied sound signal affects the buildup of the induced effect, could be a direct comparison between effects induced via notched noise and via notched music during both states, wakefulness and sleep.

4.4.2. Result 2: Increased activation for the within-notch range

The increased activation found after notched-noise exposure supports the finding of study 1 (Kaiser & Schoenwiesner, 2017, in prep.), but varies from the detected decrease in activation, which was reported in all studies by the group around Pantev (e.g., Okamoto, Stracke, Stoll & Pantev, 2010; Pantev et al., 1999, Stein et al., 2015a,b). As discussed in study 1 the varying results across studies could either be interpreted as addition to one another or as contradicting outcomes. Before describing these two interpretations in more detail, it is important to point out that both groups tested different areas relative to the notch. While all

studies by Pantev and colleagues tested effects for the frequency at the notch centre, the two studies by Kaiser and Schoenwiesner tested effects for frequencies below and above the notch centre. The varying results (induced increase vs. decrease in cortical activation) could be considered as an addition in a sense that the decreased activation at the notched centre might evoke increased activations for the adjoined areas. On the other hand, the results could indicate contradicting outcomes based on the idea that the induced changes would induce linear changes across the notched frequency band. Which means that increased activations below and above the notch centre would consequently indicate elevated activations at the notch centre. A clear support for either interpretation could only be obtained by direct measures of all involved notch areas (i.e., testing effects at the notch centre as well as above and below the notch centre). The current study could have already given such an opportunity, however, we resigned from any design changes to allow for a more direct comparison between the outcomes of the current study with the results of our study on notched music listening during wakefulness.

4.4.3. Result 3: Effect limited to lowest frequency in the within-notch range

The results of the current study support the outcome of study 1 that notched sound exposure creates an increase in cortical activation for test frequencies. However two findings differ between both studies. In study 1 effects of notched-music listening were found for both notch ranges, within and below the music notch, with an increased activation for test frequencies in 1 octave distance to the edge frequency (250 Hz and 1000 Hz). In the current study effects were detected for the lowest within-notch frequency, that is the test frequency in 0.5 octave distance to the edge frequency (707 Hz). Furthermore, effects of notched-noise

exposure were limited to the within-notch range. No changes were detected for the below-notch range, within or across test frequencies. These differences between the two studies might be based in the differing duration of the noise-manipulation. That is, after only several hours of notched sound exposure, the induced effect might be limited to the notch range, while more widespread changes could develop over time.

As mentioned earlier, the current study was performed with the identical design as the adaptation test performed in study one to allow for direct comparison across studies. However certain limitations have to be pointed out. First the electrode montage between both studies differs, which had some effects on the performed data analyzes. While the application of 64 electrodes in study 1 allowed for whole-head analyzes, ROI analyses had to be performed in the current study based on the limited number of electrodes used for recording. The study design itself prevented the application of a larger montage. The post-test should be performed without delay directly after the sleep recording, and pre- and post-test sessions had to remain identical. The same montage, used during the night recording, was therefore also applied for the test recordings. As pointed out above, in the discussion section of the previous sleep study, the usage of the electrode paste prevents the application of additional electrodes beyond the 10-20 system. The ROI was therefore limited to six frontal and central electrodes. Another limitation is the sample size. While 16 participants performed the notched music training in study 1, only 10 participants were tested in the current study. A larger number of participants would have been preferable, however, as sleep testings are more demanding in terms of temporal and financial aspects, additional testings had to be waived. Despite these limitations, comparisons across studies are still feasible, and raise interesting questions for future research. The most evident one, how do effects induced around the notch centre relate

to effects at the centre. Furthermore it would be of great interest to test how the effect of notched-noise exposure evolves throughout the night, and, whether whole-night exposure to notched-music would induce similar strong effects as found for notched pink noise.

Taking together, the present study showed, for the very first time, that several hours of notched-noise exposure during night sleep is sufficient to induce changes in cortical frequency processing. This outcome is of special interest as it does not only support the claim that information can be perceived and processed during sleep, it also strengthens the idea that the induction of change, and therefore learning as such, are possible while sleeping. Future research should aim for a better understanding of sleep, and its possibilities.

CHAPITRE 5:

General Discussion

This thesis aimed to investigate auditory frequency processing during sleep, relative to wakefulness. Frequency processing was ascertained via adaptation, in the form of adaptation release responses. In the following I will discuss the outcomes of the presented three studies focussing on three main topics: (1) the effects of notched sound exposure, (2) frequency processing during sleep, and (3) the impact of sleep on EEG measures.

5.1. Notched sound exposure

Two studies tested the effects of an auditory manipulation, which has been proposed and extensively tested, by the group around Pantev. The manipulation is based on the idea that repeated listening to notched music will alter the cortical processing of the notched frequencies. In a number of studies Pantev and colleagues demonstrated a decreased activation at the notch centre after music listening periods ranging from 3 days (Pantev, Wollbrink, Roberts, Engelien & Lütkenhöner, 1999; Stein et al., 2015a, b) to a couple of months (e.g., Okamoto, Stracke, Stoll & Pantev, 2010). Despite the large number of studies performed on notched music listening, the induced effects are still not fully understood. The existing research focused solely on effects at the notch centre, and was exclusively performed by the group around Pantev. Based on these limitations we designated one study to test the proposed effects of notched music listening. We aimed to gain a better understanding of the induced

effects by expanding the research focus within the music notch, as well as testing frequencies outside the music notch. In addition, our first study was also used to compare two measures of cortical frequency processing, aiming to select a sensitive measure, and to establish the design for our second notch study, which was performed to test the effects of notched sound exposure during sleep.

Results of the first study, notched music listening during wakefulness, provided new insights on the effects of notched music listening. For the first time it was demonstrated that the induced effect spreads to frequencies outside the notch. Furthermore, the induced effects in our music-listening study resulted in an increased cortical activation, rather than the proposed decrease. In line with this result, an increased activation after notch sound exposure was also found in our second notch study. As discussed above more research is needed to identify the reasons for the varying effects of notched music listening (i.e., increase versus decrease in cortical activation). One possible explanation for the found differences might be that the positions of the tested frequencies differed across studies. While Pantev and colleagues tested the notch centre, our two studies tested frequencies below and above the notch centre. Assuming that the frequency position is of relevance would imply that the effect at the notch centre differs greatly from effects around the notch centre. Whether notched music listening can induce such sharp changes in the frequency tuning of the stimulated cells remains a question for future research. Independent of the reasons for the varying effects, the found differences and the detected spreading of the induced cortical changes are crucial, especially for clinical applications of notched music listening, like the proposed Tailor-Made Notched Music Training (TMNMT), developed by Pantev and colleagues to treat tinnitus (e.g., Teismann, Okamoto & Pantev, 2011, Stein et al., 2015a,b; Wunderlich et al., 2015).

The demonstrated spreading could not only affect or limit the sought-after outcome of such a tinnitus treatment, they might even lead to new malfunctioning. Furthermore, the induced increase in cortical activation, found in our study, would completely counteract the suggested TMNMT. Considering these varying outcomes and the newly detected spreading of the induced effects, it becomes evident that more research is necessary to fully understand the cortical effects of notched music listening and the effect and value of related clinical applications (e.g., TMNMT).

Our third study was used to test whether cortical plasticity could be induced during sleep. Following the design of our first study, we presented a notched sound signal to sleeping participants throughout one night. The sound signal consisted of notched noise rather than notched music. Results demonstrated, for the first time, that exposure to notched noise can induce cortical changes during sleep. This finding indicates that the sleeping brain is able to process auditory frequency information. It also indicates that auditory processing during sleep remains rather precise and impactful. That is, the processing remains precise enough to detect the notch within the sound signal, and that the missing frequency information has a strong enough impact to induce changes in the cortical processing of the notched frequencies. While the second notch study indicates that frequency information can be processed during sleep, its main finding clearly is that changes in cortical frequency processing can be induced during sleep. This result is in line with a small number of studies demonstrating that new information can be acquired during night sleep.

Finally, the results of both notch studies suggest that effects within and outside the notch might not be induced simultaneously, or with identical strength, as no changes were detected in the below-notch range after one night of notched noise exposure. However the

missing effect in the below-notch range could also indicate sleep-specific differences in a sense that notch-related activations are less widespread and remain more local during sleep relative to wakefulness. Research on network activity during whole night sleep is still rather sparse, as the application of higher resolution techniques like fMRI or MEG are known to affect sleep. The noise level as well as the spatial constraints of these techniques create an unnatural sleeping environment and affect the sleep quality. The same is true for higher resolution EEG. The application of an electrode cap allows for a denser electrode placements, however, such a cap is rather uncomfortable and might affect sleep (Huber, Ghilardi, Massimini & Tononi, 2004). Research on activity patterns and network activity during sleep is therefore most often limited to a few hours of sleep at the beginning of the night. Larson-Prior et al. (2009) analyzed functional connectivity during light NREM sleep via several 20 min long fMRI recordings during night sleep. The authors reported little to no sleep related changes in functional connectivity for the tested sensory and cognitive networks, but noted that connectivity might be more affected during deeper NREM sleep and REM sleep. Massimini et al. (2005) applied high-density EEG and TMS (transcranial magnetic stimulation) to evoke cortical responses and to measure sleep related changes in the distribution of the evoked activity. Results indicate that the evoked activation remain more local during light NREM sleep relative to wakefulness, which is interpreted by the authors as a 'break-down' of effective connectivity during sleep. While both studies show different effects of sleep on the measured connectivity, it remains unclear how neural networks and activity patterns change during later sleep stages and during whole night sleep. Related to our study, the question whether notch-related activations are less widespread and remain more local during sleep relative to wakefulness, or whether the below-notch effects needs more time to

built up, could be tested, for example, by extending the test design from one test night to a number of subsequent test nights. Such a study could still not test sleep related changes on functional connectivity during whole night sleep directly, however it could give some indications on the built-up of the induced effect.

5.2. Frequency processing during sleep

The results of the first sleep study (article 2 in this thesis) demonstrate that cortical changes in frequency processing can be induced during sleep. This outcome is a strong indication that frequency information is processed during sleep. Furthermore it suggests that the processing was not just superficial but remained precise and effective during sleep. It was sensitive enough to detect the notch within the presented sound signal, and the missing frequency information was relevant enough to induce cortical changes. While the induced notch-effect clearly shows that frequency information is processed during sleep, we failed to measure frequency specific responses directly during sleep. In our second sleep study (article 3 in this thesis) frequency specific responses were measured in form of adaptation release responses, and were recorded during wakefulness and sleep. Frequency specific responses differed during wakefulness but not during sleep. As pointed out before, the missing response differences during sleep can be interpreted in two ways. They could either indicate that adaptation functions differently during sleep relative to wakefulness, or they could indicate that the applied measure was unable to detect response differences during sleep. The first interpretation assumes sleep-related differences for adaptation itself. Adaptation during sleep could either built up slower or be less strong in general. Both would imply that cells respond less strongly to a presented signal during sleep relative to wakefulness, which results in a less

strong adaptation. Edeline and colleagues showed sleep related changes in the frequency sensitivity and responsiveness of auditory thalamic cells, and to some extend for auditory cortical cells (Edeline, Manunta and Hennevin, 2000; Edeline, Dutrieux, Manunta & Hennevin, 2001). Edeline, Manunta and Hennevin (2000) argue that the reduced responsiveness of a cell causes a reduction of its receptive fields and therefore an increase in its frequency selectivity, as weaker evoked responses diminish and disappear towards the outer borders of the receptive field. Such an increased frequency selectivity would be relevant for adaptation, and would affect the measured adaptation release responses. A higher frequency selectivity would lead to a reduced number of neurons that adapt to the adaptation tone, and to a reduced number of unadapted neurons that would be activated by the probe tone, which both would result in a decreased adaptation release response. Such a decreased adaptation release response might have been too weak to detect, which brings us to the second interpretation of the missing response differences. The missing differences could indicate that the applied measure was not able to detect differences between stimulus responses during sleep. As pointed out in the discussion section of that study, sleep-specific changes in the EEG signal are most likely to alter the outcome of any applied measure. Such sleep specific changes are, for example, the increased background activity that accompanies most sleep stages, as well as changes in amplitude and latency of ERPs during sleep relative to wakefulness. Whether the missing response differences in the current study are based in sleep-related changes of adaptation, or in sleep-related effects on the applied measure lies unfortunately outside the scope of the current thesis, but provides an interesting question for future research.

5.3. The impact of sleep on EEG measures

These sleep-specific changes in the recorded signal are in fact of great relevance for any study that applies ERP measures during sleep. Sleep-specific components like K-complexes and spindles have an undeniable impact on the EEG signal and the obtained ERP waveform, however their mechanisms and functions are not fully understood. This is especially crucial as today's sleep research focuses on ERPs that are known from the awake state and aims to detect them in the signal of the sleeping brain. The differences between EEG signals of wakefulness and sleep are hereby approached in two different ways. Either by aiming to minimize the differences between the awake and the sleep signal, or by focussing on sleep-specific activations and their impact on the obtained ERP. In the first approach, sleep specific activations are tend to be considered as noise, and the sleeping state itself as a state with an increased noise-level (e.g., Nielsen-Bohlman, Knight, Woods & Woodward, 1991). In line with this idea it has been shown that applying a stricter high pass filter will enhance the detectability of MMN during NREM-3 sleep, while having little effect on the MMN during wakefulness (Sabri & Campbell, 2002). Related to the second approach it has been reported that MMN could be measured during NREM-2 sleep, however only when analyzing trails that contained K-complexes which were elicited by deviant stimuli (Sallinen, Kaartinen & Lyytinen, 1994). An interesting suggestion that points in a different and new direction comes from Winter et al. (1995) who hypothesizes that information processing is state-specific. That is, information processing might be performed by different systems, one specific to wakefulness and one specific to sleep or light sleep, and that the processing of each system elicits different ERPs. Following this idea we should not aim to improve the detection of

awake-ERPs during sleep, but should start investigating the ‘sleep system’ and its related sleep-ERPs. However, such sleep-ERPs are nearly impossible to detect without direct feedback of the sleeping participant. Yet, Winter’s proposition is still of relevance, as it strongly suggests that the differences between awake and sleep ERPs should not be underestimated. While applying stricter filters, or focussing on specific sleep components might help to reduce the difference between the sleep and the awake signal, it might also prevent us from detecting information processes that are sleep specific. Furthermore, the failure to detect certain awake ERPs during sleep should not be considered as a prove that the underlying process does not exist. These and other challenges make the still rather young research field of information processing during sleep extremely interesting, and personally I hope that more and more research will take on the challenge and help to tackle it.

Taking together, the present thesis provides new proof that the sleeping brain is capable to perceive and process auditory frequency information, and that auditory plasticity can be induced during whole night sleep. Furthermore, our results indicate that adaptation, might function differently during sleep than it does during wakefulness. While our results extend existing research, they also raise numerous new questions. More research is needed to fully understand which information can be processed during sleep and how processing during sleep differs from information processing during wakefulness. Such research could be of importance for clinical applications as well as day to day life. Although the dream to learn a new language while sleeping might remain only dream, a better understanding of information processing during sleep could lead to the development of training programs that activate and stimulate specific brain regions or modify certain aspects of information processing, like sound

discrimination, or detection while sleeping. I hope that future research will reveal the potential of the sleeping brain, and fully expel the still existing assumption that the sleeping brain is isolated and unresponsive.

Thank you.

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