JYVÄSKYLÄ STUDIES IN EDUCATION, PSYCHOLOGY AND SOCIAL RESEARCH

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Esitetään Jyväskylän yliopiston yhteiskuntatieteellisen tiedekunnan suostumuksella
julkisesti tarkastettavaksi yliopiston Villa Ranan Blomstedt-salissa
huhtikuun 19. päivänä 1997 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Social Sciences of the University of Jyväskylä
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UNIVERSITY OF JYVÄSKYLÄ

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Publishing Unit, University Library of Jyväskylä

URN:ISBN:978-951-39-8063-4
ISBN 978-951-39-8063-4 (PDF)
ISSN 0075-4625

ISBN 951-34-0959-7
ISSN 0075-4625

Jyväskylä University Printing House,
Jyväskylä and ER-Paino Ky, Lievestuore 1997

ABSTRACT

Sallinen, Mikael
Event-related brain potentials to changes in the acoustic environment during sleep and sleepiness
Jyväskylä: University of Jyväskylä, 1997, 104 p.
(Jyväskylä Studies in Education, Psychology and Social Research,
ISSN 0075-4625; 124)
ISBN 951-34-0959-7
Yhteenveto: Aivojen herätevasteet muutoksiin kuuloärsykesarjassa unen ja uneliaisuuden aikana.
Diss.

The experiments in this study were designed to examine the processing of auditory stimuli by young human adults during sleep and sleepiness. Event-related brain potentials (ERPs) were used to indicate the stimulus processing. The focus was on an ERP response termed mismatch negativity (MMN), which has been thought to represent a pre-attentive response to a change in the acoustic environment. Experiment I suggested that MMN occurs as a response to a pitch change (20%) during stage 2 sleep, but only when the pitch deviation also elicits a K-complex. Experiment II showed that the appearance of a K-complex to a pitch change is preceded by an increase in the susceptibility of the brain to the pitch change and to the standard tone that immediately precedes the pitch change. The MMN-like deflection appeared in association with the elicitation of the K-complex when the pitch deviation was small (10%) but not when it was large (100%). Study III showed a P3b-type wave to a large pitch change (100%) during tonic, but not phasic rapid eye movement (REM) sleep. No MMN appeared during REM sleep. Experiment IV demonstrated that the MMN recorded under optimal stimulus conditions was attenuated even before actual sleep, during sleepiness. The results suggest that i) traditionally categorised sleep stages contain microstates and substages which systematically differ in terms of the processing of auditory events and ii) the highly automatic processing of an auditory stimulus change indicated by MMN declines already during sleepiness, even though the elicitation of full-amplitude MMN may be possible during some microstates of sleep.

Keywords: auditory event-related potentials, human sleep, microstates, sleepiness, MMN, P3b, K-complex

ACKNOWLEDGEMENTS

The present work has required the flexible co-operation of many people. Without the willingness of these people to participate in my research project, I would not have been able to realise my ideas and elaborate on them.

First and foremost, I would like express my gratitude to my supervisor Professor Heikki Lyytinen for his guidance and support during various phases of the project. I would particularly like to thank him for his ability to know when to offer guidance and when to give me responsibility.

I am also grateful to my thesis referees, Professor Risto Näätänen and Professor Heikki Lang for their constructive criticism and their encouraging attitude toward my studies. My thanks also go to Professor Carl Hagfors and Dr. Tapani Korhonen, who belonged to my guidance group.

Jukka Kaartinen's contribution to my research project has been invaluable. I thank him for his guidance, especially with respect to numerous methodological issues, and for his scoring of the sleep stages. His enthusiasm about psychophysiological sleep research has also inspired me in many ways.

Taisto Leppäsaari patiently taught me to use the computer-based program needed for the electrophysiological recordings and data analysis. I thank him for his contribution and also for sharing my problems with the project.

Asko Tolvanen has been an irreplaceable person in the statistical analysis of the data. I am particularly grateful for his calm attitude during the times when the statistical problems seemed to be insurmountable.

My thanks also go to Lauri Viljanto, Heikki Melkinen, and Timo Rossi, all of whom assisted with the instrumentation.

I am also indebted to the subjects of my studies. The last experiment was especially exceptionally demanding for the subjects because it required them perform a boring task over night.

Finally, I wish to express my warmest gratitude to my wife Kirsi, who spent approximately 70 busy evenings and nights with our small children, Anni and Juho, when I was working in the sleep laboratory.

Vantaa, March 1997

Mikael Sallinen

LIST OF PUBLICATIONS

This thesis is based on the data presented in the following articles, which are referred to in the text by their Roman numerals (I-IV).

I Sallinen, M., Kaartinen, J., & Lyytinen. H. (1994). Is the appearance of mismatch negativity during stage 2 sleep related to the elicitation of K-complex? *Electroencephalography and Clinical Neurophysiology*, 91, 140-148.

II Sallinen, M., Kaartinen, J., & Lyytinen. H. (in press). Precursors of the evoked K-complex in event-related brain potentials in stage 2 sleep. *Electroencephalography and Clinical Neurophysiology*.

III Sallinen, M., Kaartinen, J., & Lyytinen. H. (1996). Processing of auditory stimuli during tonic and phasic periods of REM sleep as revealed by event-related brain potentials. *Journal of Sleep Research*, 5, 220-228.

IV Sallinen, M. & Lyytinen. H. (in press). Mismatch negativity during objective and subjective sleepiness. *Psychophysiology*.

CONTENTS

1 GENERAL INTRODUCTION

The four studies included in this project were designed to examine brain responses to auditory stimuli during sleep and sleepiness, which are characterised by reduced behavioural responsiveness to and decreased conscious awareness of external events. These features are essential so that a person can fall asleep during sleepiness and the brain has a chance to recuperate from waking time activity. Several studies have shown that disrupted nocturnal sleep leads to daytime sleepiness and impaired performance in various mental tasks (Bonnet, 1985, 1989). External stimuli are not, however, totally blocked out in sleep; this circumstance is biologically meaningful because otherwise it would be impossible to be awakened by any external event as is so when a person is in coma. Thus a person asleep is put in a contradictory situation when presented with a stimulus. He or she faces both a demand to awake and a demand to continue sleep.

Whether or not a sleeping person is awakened by a sound is largely determined by the strength of the sound but possibly also by its quality (Koella, 1969; Poitras et al., 1973; Strauch and Schneider-Düker, 1978; Zung & Wilson, 1961). Another essential determinant is the prevailing sleep stage during the moment of stimulus. Traditionally, sleep is categorised into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Rechtschaffen & Kales, 1968). NREM sleep contains four stages labelled stage 1, 2, 3, and 4. Stages 3 and 4 are often combined, and this combination is called slow wave sleep (SWS), referring to large amplitude waves (>75μV peak-to-peak) with low frequency (<2Hz) in electroencephalography (EEG) during these stages. The arousing effect of an auditory stimulus has been shown to decrease progressively from stage 1 sleep to stage 4 sleep (Poitras, Thorkildsen, Gagnon, & Naiman, 1973; Zung & Wilson, 1961). In REM sleep, called also paradoxical sleep (PS), the threshold has been shown to be lower than in SWS (Poitras et al., 1973; Rechtschaffen, Hauri, & Zeitlin, 1966; Strauch & Schneider-Düker, 1978). Interestingly, SWS has also been proposed to comprise the most essential sleep stages in terms of recuperation (Horne, 1988). In addition to the transition from SWS to stage 1 sleep, the awakening threshold decreases with ageing (Busby, Mercier, &, Pivik, 1994; Zepelin, McDonald, & Zammit, 1984)

and with the need to be awakened by external events (e.g., after giving birth) (Poitras et al., 1973). The awakening threshold has also been reported to decrease throughout the night (Rechtschaffen et al., 1966; Watson & Rechtschaffen, 1969); this phenomenon has been assumed to result from a decrease in sleep pressure (Lammers & Badia, 1991).

The connection to the external environment starts to attenuate even before a person reaches an actual sleep stage (i.e., during sleepiness). This impairment is characterised by an increased unevenness in responding to attended stimuli. The occurrence of so-called lapses or blocks or pauses (response omission or unusually long reaction time) was a prominent finding in early studies of the effects of sleep deprivation on cognitive functions (Warren & Clark, 1937; Williams, Lubin, & Goodnow, 1959). These lapses occur frequently in connection with microsleep (Bjerner, 1949). The number of lapses increases as sleepiness become more severe due to an increased time awake (Dinges & Kribbs, 1991; Williams et al., 1959). In addition, an increase in the standard deviation of reaction times simultaneously with an increase in the mean reaction times is typical of sleepiness (Dinges & Kribbs, 1991).

1.1 Processing of external events during sleep: different measures

The question of interest in the present thesis is the cortical processing of external stimuli when they do not result in awakening. In this context, questions as how capable a sleeper is of i) detecting external stimuli, ii) discriminating between external stimuli, and iii) forming associations between stimuli (i.e., learning) have been the objectives of several related studies. In addition, researchers have examined whether various sleep stages differ in terms of these abilities.

The processing of non-awakening stimuli can be studied by using either subjective, behavioural or physiological measures. One subjective method is to awake sleeping subjects and ask them whether they have detected an external stimulus while sleeping. Using this method, Lasaga and Lasaga (1975) found that subjects' ability to recall or recognise words impaired progressively from stage 1 and REM sleep to SWS. Some sort of recognition was, however, possible even after the subjects awoke from SWS. Another alternative subjective method is to ask subjects to report the contents of the dream that occurred immediately prior to awakening. Afterwards the dream report can be analysed to determine whether stimuli presented during sleep can be identified. Studies have shown that auditory stimuli can be incorporated into dreams during both stage 2 and REM sleep (Burton, Harsh, &, Badia, 1988; Hoelscher, Klinger, &, Barta, 1981). This incorporation occurs in about 40% of trials in which a subject reports sleep mentation during both stage 2 and REM sleep.

Another possible means for examining stimulus processing during sleep is to measure behavioural responses to external events. Numerous studies have demonstrated that a sleeping subject is able to respond to a sound during both NREM and REM sleep by pressing a microswitch (Burton et al., 1988; Ogilvie &

Wilkinson, 1988; Williams, Morlock, & Morlock, 1966) or by taking a deep breath (Badia, Harsh, Balkin, Cantrell, Klempert, O'Rourke, & Schoen, 1984; Badia, Harsh, Schoen, Balkin, Alexander, & Cantrell, 1981). During sleep, the respiratory response is easier to elicit than the microswitch closure response is. This difference is probably due to the fact that the respiratory system is active also during sleep. The probability of responding is at its lowest level during SWS when measured with either respiratory (31% for stage 3 and 17% for stage 4) (Badia et al., 1984) or microswitch closure (0-5%) (Ogilvie & Wilkinson, 1988; Williams et al., 1966) responses. In the same studies, the corresponding probability has been shown to be the highest during stage 1 sleep (70% - 80%). A marked drop in the probability of microswitch closure responses occurs after a person enters stage 2 sleep (25%). This drop is not so clear for respiratory responses, whose probability for stage 2 sleep is over 60%. The level of behavioural responsiveness can be markedly increased within all sleep stages when response production is facilitated by reinforcement procedures (Badia et al., 1984; Williams et al., 1966). On the other hand, one should have a cautious attitude towards these differences because the categorisation of sleep into clear-cut stages is arbitrary.

Interestingly, Burton et al. (1988) found a negative association between subjective and behavioural measures of stimulus processing during sleep. The likelihood of the respiratory response was lower in trials during which the subjects incorporated an external stimulus into their dreams. The authors' interpretation was that, in the case of incorporation, a stimulus is integrated into a dream so successfully that the stimulus loses its disturbing characteristic. Thereafter a behavioural response to a stimulus is not needed because it is a part of the dream. In other words, it is difficult to use either behavioural or subjective measures alone when the occurrence of elaborated stimulus processing is being assessed during sleep.

The third method for examining stimulus processing during sleep is to measure stimulus-elicited physiological events. These psychophysiological responses can be divided into autonomic and central nervous system responses (ANS and CNS responses, respectively). Studies have shown that both types occur during sleep. CNS responses will be dealt with more extensively in the following separate section. The most popular ANS responses in this context have been cardiovascular and electrodermal responses. The most used cardiovascular measures are heart rate (HR) and plethysmographic finger pulse amplitude responses. The corresponding electrodermal measures are skin conductance and galvanic skin resistance responses. The electrodermal responses have been shown to be markedly attenuated during sleep compared with wakefulness (Johnson & Lubin, 1967). The likelihood of electrodermal responses significantly increases when an electroencephalographic (EEG) response called the K-complex (for a review of the K-complex, see Section 1.2.2.3) occurs to a stimulus (Johnson & Lubin, 1967). The cardiovascular system seems to be very responsive to external stimuli during sleep. The main finding has been that a sleeping subject is more responsive to external stimuli during stage 2 and REM sleep than during SWS when measured by the HR response (Hord, Lubin, & Johnson, 1966; Johnson & Lubin, 1967). This finding

is in agreement with those of most of the afore-mentioned studies that used subjective and behavioural measures. HR responses may also provide an opportunity to evaluate the function of stimulus processing during sleep. Berg, Jackson, and Graham (1975) found that a tone primarily elicited an accelerative HR response in sleep. Their interpretation was that an external stimulus does not elicit an orienting response (OR) during sleep but instead produces a defensive response (DR) which heightens the arousal threshold and thus facilitates the maintenance of sleep.

1.2 Processing of external events during sleep: CNS responses

The most used direct CNS measures of stimulus processing are stimulus-elicited changes in the EEG. These changes usually occur within 1 s after an eliciting event. The stimulus-elicited EEG changes are often so small in amplitude that they are masked by the ongoing EEG. An effective technique to separate these stimulus-elicited events from spontaneous ones is to average EEG epochs (trials) collected around critical stimuli. Because stimulus-elicited events are time-locked to the presented stimulus in contrast to spontaneous events, the former become separable after a sufficient number of trials are averaged. The average curves are called event-related (brain) potentials (ERPs). ERP waves are usually classified according to their scalp distribution, peak latency and polarity. In the following text, ERP waves have been divided into early, middle, and late latency types (see Picton, Hillyard, Krausz, & Galambos, 1974), the emphasis being on the late waves because they are the subject of this thesis.

1.2.1 Early and middle ERP waves

The early ERP waves to auditory stimuli occur within the first 10 ms after an eliciting event. They reflect stimulus-elicited activity in the acoustic nerve and auditory brainstem pathways. Many studies have shown that these responses are independent of attention (e.g., Connolly, Abur, McGillivary, & Scott, 1989; Hackley, Woldorff, & Hillyard, 1990; Hirschorn & Michie, 1990). The effects of sleep on the early ERP waves have been found to be marginal (Amadeo & Shagass, 1973; Bastuji, Garcia-Larrea, Bertrand, & Mauguière, 1988; Campbell & Bartoli, 1986). The small latency changes found during nocturnal sleep have been more associated with body temperature variations during the night than with any particular sleep stage (Bastuji et al., 1988; Litscher, 1995). These results suggest that an impairment of conscious awareness of auditory stimuli during sleep is not due to the inhibition of stimulus processing at the peripheral or brainstem level.

The middle-latency ERP waves occur within the latency range of 10-50 ms and have either thalamic or cortical generators. Some results suggest that these ERP waves may be affected by attention (McCallum, Curry, Cooper, Pocock, & Papakostopoulos, 1983; Woldorff, Hansen, & Hillyard, 1987). Some recent

evidence supports the view that the middle ERP waves are influenced by sleep when clicks are presented at a fast rate. Campbell, Bell, and Bastien (1992) reported that the Na-Pa complex, which occurs at a 15-30 ms latency, declines in stage 2 and REM sleep when eliciting stimuli are presented at a rate of 16 clicks/s but not when the same stimuli are presented at a rate of 1 click/2 or 8 s. Deiber, Ibanez, Bastuji, Fischer, and Mauguière (1989) also found a decrease in the amplitudes of the Na and Pa waves during NREM sleep (stage 2 and SWS) but not during REM sleep. They also observed an increase in the latencies of these waves and a change in scalp distribution. In their study, the interstimulus interval (ISI) was short (190-290 ms). In addition to the Na/Pa complex, the later Pb potential peaking at about 50 ms has also been reported to attenuate in NREM sleep but not in REM sleep (Deiber et al., 1989; Erwin & Buchwald, 1986).

In summary, these results suggest that the inhibition of auditory processing commences within the latency range of the middle ERP waves, particularly during NREM sleep, and that the inhibition takes place when a sensory input has arrived in the auditory cortex or even before. Thus middle latency ERP waves indicate that the effects of attention and sleep on stimulus processing begin at approximately the same time. Campbell et al. (1992) has assumed that the rejection of auditory input commences within 25 ms after stimulus onset during sleep. This latency is similar to the latency of the effect of selective attention (15 ms) on ERPs (Hackley, 1993). The correspondence between the latency of effects of sleep and attention on ERPs does not, however, necessarily mean that the underlying mechanism would be the same in both cases.

1.2.2 Late ERP waves

Late ERP waves are considered to start 50 - 80 ms after an eliciting event. In this response category, ERPs have been labelled N1 (peaking at about 100 ms), P2 (200 ms), N2 (250 ms), and P3 (300 ms) on the basis of waves observed during wakefulness. The Pb or, interchangeably, P1 has also been considered as a late wave by some researchers (e.g., Picton et al., 1974). The direction of attention is known to have a considerable effect on ERPs within the latency range of these waves. In sleep, ERPs also contain long latency waves that do not appear in waking ERPs. These sleep-specific deflections are mainly associated with the elicitation of the large amplitude waveform called the K-complex during NREM stages 2, 3, and 4. During REM and NREM stage 1, ERPs have consistently been found to be similar to ERPs in wakefulness (Bastuji, Garcia-Larrea, Franc, & Mauguière, 1995; Weitzman & Kremen, 1965; Williams, Tepas, & Morlock, 1962).

The N1 wave is elicited by both attended and unattended stimuli in wakefulness and thus it can be considered to be an obligatory response to an external stimulus in wakefulness. It has been suggested that the N1 wave would be greater to attended stimuli than to unattended ones (Hillyard, Hink, Schwent, & Picton, 1973) but an alternative explanation for this effect has also been presented (Näätänen & Michie, 1979). It suggests that an attended

stimulus elicits another negative deflection that overlaps the N1 wave in certain stimulus conditions. In sleep, the N1 amplitude has been found to attenuate (Bastuji et al., 1995; Campbell, McGarry, & Bell, 1988; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Paavilainen, Camman, Alho, Reinikainen, Sams, & Näätänen, 1987; Winter, Kok, Kenemans, Elton, 1995). The latency of the N1 wave has been found to either remain stable (Nielsen-Bohlman et al., 1991) or increase somewhat (Bastuji et al., 1995) during sleep in comparison with wakefulness. Most of the studies that have shown the decline of the N1 wave during sleep have also demonstrated an increase in the amplitude of the P2 wave during stage 2 sleep (Bastuji et al., 1995; Campbell et al., 1988; Nielsen-Bohlman et al., 1991; Winter et al., 1995). The data of Bastuji et al. (1995) show a similar but less pronounced phenomenon for REM sleep.

Next, three responses studied in the present investigation are introduced in more detail. They are mismatch negativity (MMN), P3 wave, and K-complex. The first two are responses that occur in wakefulness, and previous studies have attempted to clarify their occurrence in sleep, whereas the K-complex is a sleep-specific response.

1.2.2.1 Mismatch negativity in wakefulness

The MMN response, which has been separated from the N2 wave by Näätänen, Gaillard and Mäntysalo (1978), has negative polarity above and positive polarity below the Sylvian fissure in recordings using the nose as a reference (Alho, Paavilainen, Reinikainen, Sams, & Näätänen, 1986). Usually the peak latency range and amplitude of the MMN are 100 - 200 ms and 2 - 5 μV, respectively, depending on the features of the eliciting stimulus change. It reaches maximum amplitude at the frontal electrode locations, but a clear MMN response can also be recorded centrally and above the auditory cortex (for a review, see Näätänen & Michie 1979). The MMN component is detected the most easily in the so-called difference wave, which is formed by subtracting ERPs to a repetitive standard stimulus from ERPs to a rare deviant stimulus. It usually overlaps the N1 wave, and, in the case of a marked difference between the standard and deviant stimulus, it is also overlapped by the N2b wave which has a more posterior scalp distribution when compared with MMN.

The MMN response has been shown to occur to various types of changes in an auditory stimulation (e.g., Aaltonen, Niemi, Nyrke, & Tuhkanen, 1987; Lyytinen, Blomberg, & Näätänen, 1992; Näätänen et al. 1978; Näätänen, Jiang, Lavikainen, Reinikainen, & Paavilainen, 1993; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987a; Näätänen, Paavilainen, & Reinikainen, 1989; Näätänen, Schröger, Karakas, Tervaniemi, & Paavilainen, 1993; Paavilainen, Karlsson, Reinikainen, & Näätänen, 1989; Tervaniemi, Maury, & Näätänen, 1994). No convincing evidence for the MMN response to changes in visual (e.g., Nyman, Alho, Laurinen, et al., 1990) or somatosensory (e.g., Hari, Hämäläinen, Hämäläinen, Kekoni, Sams, & Tiihonen, 1990) stimulation has been presented. The MMN has been proposed to originate from a comparison process between the short-lasting memory-trace of a frequent standard

stimulus and the sensory input of an infrequent, physically deviant stimulus (Näätänen, 1990, 1992). Thus, according to the memory-trace hypothesis, MMN is not a response to the deviant stimulus *per se*, but a response to a physical deviation in a train of concordant stimuli. There is a multitude of empirical evidence for this hypothesis. One of the strongest pieces of evidence is the finding that MMN disappears after the removal of the standard stimuli around the intervening deviant stimuli (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989; Sams, Hämäläinen, Antervo, Kaukoranta, Reinikainen, & Hari, 1985). Another primary piece of evidence is that MMN occurs also as a response to an intensity decrement (Näätänen et al., 1989). In this study, MMN became larger and appeared earlier as the magnitude of the intensity decrement was enlarged. If MMN is a response to a deviant stimulus *per se*, it should attenuate as the stimulus energy is reduced.

The formation and persistence of the memory-trace of a standard stimulus has been shown to be dependent on the interstimulus interval (Böttcher-Gandor & Ullsperger, 1992; Cowan, Winkler, Teder, & Näätänen, 1993; Mäntysalo & Näätänen, 1987; Sams, Hari, Rif, & Knuutila, 1993). The maximum ISI is about 10 s for the MMN response in wakefulness (Sams et al., 1993). When the ISI is longer than 10 s, no memory trace of a standard stimulus exists with which the incoming sensory input of a deviant stimulus could be compared. As mentioned, this comparison process is a necessary condition for eliciting the MMN response. Other crucial stimulus parameters in terms of MMN elicitation are the duration of the standard stimulus (Paavilainen, Jiang, Lavikainen, & Näätänen, 1993), the number of repetitions of a standard tone (Cowan et al., 1993; Imada, Hari, Loveless, McEvoy, & Sams, 1993; Sams, Alho, & Näätänen, 1983), and the variability of the interval between standard stimuli (Imada et al., 1993).

The MMN response has been suggested to have at least two main brain sources, one on the supratemporal plane of the auditory cortex and the other on the right frontal cortex (Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen & Alho, 1995; Näätänen & Michie, 1979). These sensory-specific and frontal subcomponents of the MMN response have been assumed to have different functions (Näätänen, 1990; Näätänen & Alho, 1995; Näätänen & Michie, 1979). The sensory-specific subcomponent probably reflects the automatic detection of a stimulus change that leads to the activation of the frontal subcomponent, whose function is to initiate an attentional switch to this stimulus change. A third generator of the MMN response is probably on the right lateral temporal cortex (Näätänen & Alho, 1995; see also Csépe, Karmos, & Molnár, 1987). Csépe (1995) suggested that the MMN response may also have subcortical sources on the basis of animal studies (Csépe, Karmos, & Molnar, 1988a, 1988b, 1993).

An essential characteristic of MMN has been argued to be its independence of attention (e.g., Näätänen, 1990) which dissociates MMN from the N2b wave (see Sams, Paavilainen, Alho, & Näätänen, 1985). There are numerous studies on waking subjects that support the hypothesis of MMN being an attention-independent response. Dichotic listening experiments have shown that the MMN response is similar for attended and unattended stimulus changes (Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989; Näätänen et

al., 1978, 1980). An MMN response has also been recorded when i) the subject's attention has been drawn away from the eliciting stimuli with an attention-demanding primary task (Lyytinen et al. 1992; Sams et al., 1985b), ii) no concomitant ANS response has been detected (Lyytinen et al., 1992), iii) a subject has not perceived a stimulus change (see Näätänen & Gaillard, 1983), and iv) the interstimulus interval (ISI) has been so short (51 ms) that the number of discriminations is too high for subjects to detect a single stimulus change (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987b). Recently, two studies presented results favouring the hypothesis that MMN may in some conditions be modulated by attention. Woldorff, Hackley, and Hillyard (1991) found that the MMN response to intensity decrements presented to the ignored ear was substantially smaller than the amplitude of the MMN response to the same deviant tones presented to the attended ear. They presented stimuli with short ISIs, and the deviances were so small that the subjects had to do their best to perceive the deviances presented to the attended ear. Näätänen (1991) admitted that the MMN response was attenuated in the study of Woldorff et al. but suggested that most of the decrease was due to the elicitation of N2b and processing negativity responses specifically to attended deviant tones. Secondly, Näätänen argued that the MMN response to a pitch change is not affected by attention, in contrast to the MMN response to an intensity change. In their later dichotic listening experiment, Näätänen and his colleagues indeed found that the intensity-MMN, but not the pitch-MMN, decreases when attention is strongly directed away from the eliciting stimuli (Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). Trejo, Ryan-Jones and Kramer (1995) argued, however, that the pitch-MMN is also influenced by attention. In their study, subjects attended to either a pitch deviation or narrative, both of which were presented binaurally. The subjects' task was either to increment a mental count of a certain word presented in the narrative (attend-words condition) or behaviourally respond to one of the two pitch changes of the same magnitude (attend-tones condition). The main result was that the MMN response to pitch changes was decreased when attention was directed towards the narrative. With a scalp distribution analysis, the authors tried to prove that the attenuation of the negative wave in the difference curve within the MMN latency was not attributed to the N1 or N2b enhancement in the attend-tones condition. Unfortunately, the authors did not use electrode sites where the MMN would have been minimally overlapped by other responses, as did Näätänen et al. (1993b). This procedure would have proved more convincingly that it was the MMN component that was affected by attention in the study of Trejo et al. (1995).

1.2.2.2 Mismatch negativity during sleep and sleepiness

Sleep provides conditions in which a subject reliably ignores stimuli to which the MMN response is measured. This has been a central reason for studying the MMN response during sleep. Thus far, only two studies out of five on young human adults have reported MMN during sleep. It is noteworthy that the MMN-like response was detected mainly in REM sleep. The studies showing

no MMN during sleep have not contained REM sleep. The study of Paavilainen et al. (1987) was the first which attempted to record MMN during sleep, but no MMN-like response occurred to a deviant tone of 1050 Hz embedded in a standard tone stream of 1000 Hz in any examined sleep stage (stages 1 and 2). The authors' interpretation was that their result did not mean that MMN is dependent on attention, but rather that it was related to a decrease in general cortical activation. They assumed that a clearer stimulus change would possibly have resulted in an MMN response. Later studies have not supported this assumption. Nielsen-Bohlman et al. (1991) failed to observe a significant MMN response during NREM sleep in spite of the fact that they used a large stimulus deviation (deviant 1500 Hz, standard 1000 Hz). However, because they found a small, non-significant negative shift within the latency range of the MMN response, they suggested that the appearance of MMN is masked by the large amplitude, spontaneous EEG during sleep. Winter et al. (1995) found no response comparable with MMN in stage 2 sleep even when a highly deviant stimulus change was used (small deviant 1200 Hz, large deviant 2000 Hz, standard 1000 Hz). Their explanation for the disappearance of MMN during sleep was that totally different neural systems are responsible for responding to a stimulus change during wakefulness and sleep. They found that an MMN response occurred to a stimulus change in wakefulness. In sleep, the same stimulus change elicited an N350 wave. This transition from MMN to the N350 occurred in drowsiness.

In addition to the magnitude of stimulus change, the ISI needed for the elicitation of the MMN response during sleep has been assumed to differ from the elicitation of the MMN response in wakefulness. Campbell et al. (1992) assumed that the ISI must be less than 0.5 s before full-amplitude MMN can be recorded during sleep. Using an ISI of 0.5 s, the authors found an unusually early and small MMN-like deflection during the second half of the night in stage 2 and REM sleep. The authors assumed that an ISI of this duration results in the decay of the memory trace of the standard stimulus prior to its comparison with the sensory input of the deviant stimulus. There is no sleep study in which ISI shorter than 0.5 s was used, and thus it is too early to conclude whether the duration of the memory trace of the standard stimulus is really so much shorter during sleep than during wakefulness.

Loewy, Campbell, and Bastien (1996) also observed an MMN-like wave during REM sleep. They used a small (5%) and large (100%) pitch change and an ISI of 600 ms. No MMN-like wave occurred in NREM sleep. The fact that the MMN-like deflection inverted in polarity at the mastoid channel supports the view that genuine MMN was observed in REM sleep. In the case of the large pitch change, the response was decreased in amplitude and duration, and with the small pitch change the response terminated unusually early when compared with that of wakefulness. The authors hypothesised that the decreased amplitude in REM sleep was due to an attenuation of the amplifying neuronal populations at the supratemporal auditory cortex responsible for the magnitude of the MMN response (Näätänen, 1991; Näätänen et al., 1993b). The unusually early termination of the MMN-like wave in REM sleep was attributed to the deactivation of the frontal subcomponent of the MMN

response or interchangeably to the elicitation of an N2b response in wakefulness, but not in sleep.

Promising evidence for the occurrence of the MMN response has also been found in studies with human newborns and cats as subjects[1]. Alho, Sainio, Sajaniemi, Reinikainen, and Näätänen (1990) reported on an MMN-type wave during quiet sleep in human newborns. The values of the critical stimulus parameters were comparable with the aforementioned sleep MMN studies with human adults, and thus they can not explain the difference in the occurrence of the MMN-type wave between these groups. Cheour-Luhtanen, Alho, Kujala et al. (1995) found an MMN response to a phonetic change in sleeping newborns by using /y/ as a standard stimulus and /i/ as a deviant stimulus. Näätänen and Lyytinen (1994) assumed that this possible difference between human newborns and adults may be due to the fact that sleep is a prevailing state for newborns and the differentiation between sleep and wakefulness is not so clear as in adults. Later however, Leppänen, Eklund, and Lyytinen (1997) failed to record a reliable MMN response from sleeping newborns.

Csépe et al. (1987) recorded a reliable MMN-like wave with an increased latency from the auditory cortex of cats during SWS when compared with wakefulness. This response appeared only when the probability of the deviant was at its lowest level (5%). No significant MMN response occurred at either the vertex or the association cortex. The authors recorded ERPs directly from the cortex with implanted electrodes. In wakefulness, an MMN-like response was recorded from all the electrode locations used, and its amplitude increased as the probability of the deviant tone became lower. These results suggest that the cortical distribution of the MMN response is more restricted during sleep than during wakefulness. They also refer to the possibility that especially the frontal subcomponent of the MMN response is more clearly affected by alertness than the sensory-specific subcomponent is. It is noteworthy that Csépe et al. (1987) did not measure ERPs to the deviant tone presented without the intervening standard tones. Thus they were not able to control whether or not the MMN-like wave obtained was genuine MMN. Recently, Ruusuvirta and his colleagues (Ruusuvirta, Korhonen, Penttonen, & Arikoski, 1995; Ruusuvirta, Korhonen, Arikoski, & Kivirikko, 1996a, 1996b) showed that the MMN-like deflection measured from subcortical structures of rabbits not only occurs when a deviant tone is elicited with repetitive standard tones, but also when the deviant tone is presented alone. These results throw doubt on whether the MMN-like deflection found by Csépe et al. (1987) is genuine MMN.

Only two well-reported studies have dealt with the MMN response during sleepiness in spite of the fact that sleepiness is a phase that normally occurs before wakefulness turns into sleep[2]. Winter et al. (1995) reported that an MMN response possibly occurred to a large (100%) pitch deviation during a physiologically (i.e., objectively) defined drowsy state, but not to a small (20%) one. Paavilainen et al. (1987) noted an MMN response to a small (5%) pitch

1 At the 2nd Congress of the World Federation of Sleep Research Societies in the Bahamas in 1995, Lorrain Fullum, Arcand-Bossé, and Campbell proposed that the MMN response can be seen in elderly subjects in stage 2 sleep.

change in four of six subjects during objectively defined drowsiness characterised by the slowing of alpha activity and an increase in the amount of 5-7 Hz activity. A P3a type wave following the MMN response during the reading condition was no longer significant. In their additional experiment with one subject, an MMN component could be detected only during some blocks in the drowsy state, but it disappeared totally in stage 1 sleep. In addition to these two studies, Lang, Eerola, Korpilahti, Holopainen, Salo, and Aaltonen (1995) reported data from two subjects whose subjective sleepiness and reading speed were measured during a night-time MMN recording session. The MMN amplitude varied significantly during the overnight recording session. In one of the subjects, the MMN amplitude was more strongly correlated with reading speed than with subjective sleepiness. In the other subject, the MMN amplitude decreased as subjective sleepiness decreased in spite of the fact that reading speed remain stable.

There are limitations with the studies of Paavilainen et al. (1987) and Winter et al. (1995). First of all, none of them provided optimal stimulus conditions for recording MMN during sleepiness. In the study by Winter et al. (1995), the ISI (1 s) was possibly too long for recording an MMN response in drowsiness (see Campbell et al., 1992). Secondly, Winter et al. defined drowsiness so that stage 1 sleep has to be present for at least 60% of the time. As the authors mentioned, it is possible that the attenuation of the MMN component in drowsiness is due to an abrupt change in stimulus processing during stage 1 sleep. In the study of Paavilainen et al. (1987), the difference between the deviant and standard stimulus was possibly too small for the consistent elicitation of the MMN response in drowsiness. The authors suggested that this was one probable reason for their failure to show an MMN response, at least in sleep. In addition, these previous studies on MMN during sleepiness have included only traditional electrophysiological measures. It is, however, well-known that the feeling of alertness and voluntary responding also change during the wake/sleep transition. The subjective and objective measures of sleepiness do not always match (e.g., Dement, Carskadon, & Richardson, 1978; Johnson, Freemen, Spinweber, & Gomez, 1991; Sugerman, Stern, & Walsh, 1985). From the practical point of view, it would be important to know whether the subjective feeling of alertness is associated with the impairment of MMN response. Secondly, the measurement of performance in a primary task during the recording of the MMN response would make it possible to evaluate changes in voluntary responding that are accompanied by a possible decay of MMN during sleepiness.

1.2.2.3 P3 wave

The N2 wave is followed by a positive wave in certain conditions. An ERP wave labelled P3a can occur when a stimulus change occurs among an

2 In a poster presented at the 12th Congress of the European Sleep Research Society in Italy in 1994, Loewy, Lugt, and Campbell suggested that the decline in the MMN response commences already in relaxed wakefulness (alpha EEG with slow eye movements) and it continues in stages 1 and 2 of sleep. They used small (10%) and large (100%) changes in pitch and a short ISI (600 ms).

unattended homogeneous stimulus stream. The needed intrusiveness of the stimulus change can be considered to be determined by the magnitude of a stimulus change, the attentional demands of the primary task, and the subject's level of motivation to concentrate on the primary task. When the primary task is not demanding a small stimulus change can also elicit the P3a (e.g., Sams et al. 1985b). The P3a has a frontocentral scalp distribution, and it peaks at about 250 - 350 ms. Its occurrence has been associated with an attentional switch to a change in an unattended stimulus stream that leads to an awareness of the stimulus change (Sams et al., 1985b). This interpretation is consistent with that of Verleger (1988) who has proposed that the P3a occurs to a stimulus that interrupts the ongoing cognitive activity. The P3a also occurs when the eliciting stimulus is presented in an attended stimulus stream. Courchesne, Hillyard, and Galambos (1975) found that an unannounced visual stimulus presented as a part of a visual stimulus stream including frequent non-target and infrequent target stimuli elicited a more anterior P3 than the target stimulus did. Courchesne (1978) proposed that the frontal P3 to a unannounced stimulus is associated with the inability to categorise a distinctive event when it is presented for the first time.

The P3b introduced by Sutton, Braren, Zubin, and John (1965) occurs mainly in an "attend" situation for a stimulus to which a subject is instructed to respond in some way. It may, however, occur in an "ignore" condition if the stimulus change is intrusive (Becker & Shapiro, 1980; Polich, 1986, 1989). In this case, the amplitude of the P3b is, however, lower than in the attend situation. The P3b has a parietal scalp distribution, and it peaks at about 300 - 600 ms after the onset of an eliciting event.

A widely accepted interpretation of the P3b is based on the context updating hypothesis (Donchin, 1981; Donchin & Coles, 1988; see ,however, Verleger, 1988). It argues that the elicitation of the P3b is associated with the occurrence of a stimulus that requires an update of the cognitive model of the environment. This flexibility of the cognitive model makes it possible to maintain the model in a changing environment. The context updating hypothesis suggests that the P3b-evoking stimulus is evaluated carefully and categorised. An essential finding on which the context updating hypothesis is based is that the subjective probability of the occurrence of the eliciting event is inversely proportional to the amplitude of the P3b (Squires, Wickens, Squires, & Donchin, 1976). This observation suggests that the amplitude of the P3b correlates strongly with the need for the cognitive model of the environment to be revised after an eliciting stimulus. Another essential determinant of this need is the task relevance of an event. The greater the task relevance, the larger the P3b (Donchin, 1981; Donchin & Coles, 1988; Duncan-Johnson & Donchin 1977).

The latency of the P3b is usually considered to be associated with the time required for the evaluation and categorisation of a stimulus (Magliero, Bashore, Coles, & Donchin, 1984; McCarthy & Donchin, 1981). The correlation between the latency of the P3b and the reaction time depends on the required accuracy of the stimulus evaluation and categorisation before an overt response can be given (Kutas, McCarthy, & Donchin, 1977). When the subject can respond to a

stimulus without its careful evaluation and categorisation, the correlation may be insignificant.

One reason for studying the occurrence of the P3b during sleep is to determine whether a sleeping person can use the limited-capacity system while processing external stimuli. The appearance of the P3b during sleep would mean that stimulus processing could be conscious and intentional in this state in spite of the fact that sleep is characterised by the attenuation of the connection to external events. The occurrence of this type of stimulus processing at least occasionally during sleep is supported by the aforementioned studies showing behavioural and subjective indications of stimulus processing during sleep (see Section 1.2). The occurrence of the P3b during sleep has been examined in many studies, but no convincing results have been obtained. The studies by Bastuji et al. (1995) and Niiyama, Fujiwara, Satoh, and Hishikawa (1994) are probably the most essential because they include all states of alertness and their focus is mainly on the P3. Both studies showed that a P3b-type response occurred to an infrequent deviant tone presented among frequent standard tones in NREM stage 1 sleep, but its amplitude was attenuated. Bastuji et al. (1995) also found that the latency of the P3b-type wave was increased in stage 1 sleep when compared with wakefulness. These authors observed these phenomena even before their subjects fell asleep during a presleep recording period (2200 - 2300 in the evening) when compared with a control group, whose ERPs were recorded during "full wakefulness" (1500-1900 in the afternoon-evening). The association between these changes in the P3b and sleepiness has also been found in other studies (Broughton & Aguirre, 1987; Harsh & Badia, 1989; Koshino, Nishio, Murata et al., 1993; Morris, So, Lee, Lash, & Becker, 1992). Interestingly, Harsh, Voss, Hull, Schrepfer, and Badia (1994) found that changes in the P3b during the wake/sleep transition could be more closely attributed to changes in the subjects' attentiveness, as indicated by behavioural responsiveness, than to changes in the ongoing EEG.

Bastuji et al. (1995) and Niiyama et al. (1994) found no clear P3b-type response during NREM stage 2 sleep or SWS. Bastuji et al.'s (1995) ERPs of these sleep stages were characterised by waves associated with the elicitation of the K-complex. However, there was a positive wave usually called P420 between two negative waves, "N350" and "N550". The authors assumed that the N350/P420 complex reflected a type of stimulus processing similar to that associated with the waking P3b, namely, the processing of stimulus relevance. Other researchers have connected the P420 wave even more closely to the waking P3b. Nielsen-Bolhman et al. (1991) suggested that the P420 "may correspond to the waking P3". This interpretation of the P420 was based on the findings that the two waves have similar scalp distributions and they are elicited by a deviant stimulus. Salisbury, Squires, Ibel, and Maloney (1992) stated that a P3b-like potential occurs to an intrusive and loud stimulus during stage 2 sleep although its amplitude is reduced. The main findings behind this proposal were that a P420 and a waking P3b had similar scalp distributions and latencies. According to them, the occurrence of the P3b-type response suggests that it partly reflects an "automatic, pre-attentive evaluation of deviant stimuli". Later, Salisbury (1994) presented the two-system hypothesis arguing

that two processes, namely, information processing activity reflected in the N2-P3 complex and K-complex activity reflected in the N550-P900 complex, are elicited by a deviant stimulus during NREM sleep. Harsh et al. (1994) also found that the P420 of stage 2 sleep resembled the waking P3b in terms of latency and sensitivity to a deviant stimulus. They pointed out, however, that also other positive waves, namely, P220 and P900, were sensitive to a deviant stimulus. This phenomenon could be seen irrespectively of the instructions asking subjects either to attend or to ignore the auditory input. Harsh et al. (1994) concluded that it is impossible to say whether one or more of these positive waves during stage 2 sleep reflect the same cognitive activity as the waking P3b. On the other hand, they also mentioned that the cognitive activity reflected in the P3b may be incompatible with falling asleep and with sleeping, and thus the allocation of attentional resources may dramatically change during sleepiness and sleep. Wesensten and Badia (1988) have stated that the P900 (P700 in their terminology) in sleep ERPs is a counterpart of the waking P3b. The authors found that the P900 wave to the target tone was higher in amplitude than that to the non-target tone during stage 2 sleep, SWS, and REM sleep when the probability of the target was 30%. The same held true for SWS and REM sleep but not for stage 2 sleep when the corresponding probability was 50%. Their data show, however, phenomena that argue against the hypothesis that the P900 would be a counterpart of the waking P3b. The probability of the target tone had no clear effect on the P900. Secondly, the P900 was higher in amplitude during SWS than during stage 2 sleep. As already mentioned, behavioural responsiveness is at its lowest level and the arousal threshold is at its highest level during SWS. Therefore an increase in the amplitude of the P3 during SWS would be an unexpected finding if it is thought to reflect the usage of the limited-capacity resources during SWS .

REM sleep seems to be the most potential sleep stage, together with stage 1 sleep, for the occurrence of the P3b wave. Bastuji et al. (1995) and Niiyama et al. (1994) found a positive wave with a parietal distribution for an infrequent deviant tone during REM sleep. This response was similar to the P3b recorded in wakefulness. Its amplitude was, however, smaller than that of the P3b in wakefulness in both studies. Bastuji et al. also reported that the latency (445 ms) of the P3b-type wave in REM sleep (labelled PS-P3 by the authors, PS=paradoxical sleep) was somewhat longer when compared with that in wakefulness (344 ms). The PS-P3 appeared in 73% of the ERPs that were averaged separately for each 6-min epoch. This inconsistency in the occurrence of the PS-P3 was not due to interindividual differences because each subject showed a PS-P3 during at least one recording period. In the study of Niiyama et al. (1994), the P3-type wave was detected in six of eight subjects in REM sleep. Bastuji et al. (1995) assumed that the inconsistency in the occurrence of the PS-P3 reflected the alternation of the tonic and phasic periods of REM sleep. Their data did not, however, permit one to test this hypothesis since the 6-min recording session always contained both tonic and phasic REM sleep. Their hypothesis was based on the finding that behavioural responsiveness to auditory stimuli is different during the substages of REM sleep introduced by Moruzzi (1963). Price and Kremen (1980) showed that responsiveness is at a

lower level during phasic periods that are characterised by bursts of REMs, whereas no REMs occur during tonic periods. Interestingly, studies on dream reports after tonic and phasic REM sleep suggest that the brain is more preoccupied by the ongoing cognitive activity during phasic REM sleep than during tonic REM sleep. Subjects' dreams have been found to be more active (Berger & Oswald 1962; Firth & Oswald 1975; Pivik & Foulkes 1966), to be emotionally more intense (Dement & Wolpert, 1958; Karacan, Goodenough, Sharpio, & Starker, 1966), and to have a stronger feeling of immersion in sleep mentation (Weinstein, Schwartch, & Ellman, 1988) during phasic periods of REM sleep. In addition, Taylor, Moldofsky, and Furedy (1985) observed that a decelerative HR response occurred a couple of seconds prior to a burst of REMs. The authors' interpretation was that REMs are associated with an OR to dream content. In summary, it seems that the occurrence of the P3b would be more likely during tonic than phasic REM sleep.

1.2.2.4 K-complex

The K-complex is one of the most examined phasic EEG events specific for sleep. Already in 1939 Loomis, Harvey, and Hobart found that an external stimulus elicited a distinctive, large amplitude complex of deflections in EEG during sleep. In the same year, Davis, Davis, Loomis, Harvey and Hobart reported that the same kind of pattern was present in sleep EEG when no external stimulation was administered. Later, these large amplitude transient EEG events were termed evoked and spontaneous K-complexes, respectively.

The morphology of the K-complex is defined as "a well-delineated negative sharp wave which is immediately followed by a positive component" (p. 6) in the traditional manual for scoring sleep stage by Rechtschaffen and Kales (1968). In addition to these criteria for the morphology of the K-complex, the duration of the K-complex has to exceed 0.5 s. The criterion of a minimum amplitude of 75 μV has also been widely applied although it is not mentioned in Rechtschaffen and Kales' (1968) manual. Later, Paiva and Rosa (1991) identified six types of K-complexes that differ in terms of morphology. The differentiation between these types is based on the number of separate deflections and characteristics of the EEG following the K-complex.

The K-complex occurs in NREM sleep stages 2, 3, and 4 but not in wakefulness or in REM sleep (Bastuji et al., 1995; Halász, Pál & Rajna, 1985; Nielsen-Bohlman et al., 1991; Roth, Shaw, & Green, 1956). An essential characteristic of the K-complex is that it does not occur after every stimulus presentation even when the stimulus does not vary. The probability of the elicitation of the K-complex can be increased by increasing the physical distinctiveness and lowering the probability of an eliciting stimulus (Bastien & Campbell, 1992; Niiyama, Fusimi, Sekine, & Hishikawa, 1995). The personal significance of a stimulus has also been suggested to affect the probability of the evoked K-complex (Oswald, Taylor, & Treisman, 1960), but this finding has not been confirmed by later studies (McDonald, Schicht, Frazier, Schallengerger, & Edwards, 1975; Winter, 1995). By analysing the power spectra of the pre-stimulus EEG epoch of 1.8 s, Pál, Simon, and Halász (1985)

were able to show that the elicitation of the K-complex to a stimulus depends on the brain state immediately before the stimulus is presented. The authors correctly classified 89% of their trials into K-complex and no K-complex categories on the basis of the prestimulus EEG epoch. There were several frequency components in the prestimulus EEG that differed between the response categories. The component of 24.41 Hz was the most discriminative. Its mean power was higher for the K-complex category.

In ERPs, averaged K-complexes form triphasic waveforms with components called N350, N550, and P900 (Bastien & Campbell, 1992; Campbell, Rouillard, & Bastien, 1990). There are different views concerning the relationship between the N350 wave and the N550/P900 complex. Bastien and Campbell (1992) suggested that the N350 may have to reach a certain amplitude before the N550/P900 complex can occur. They found that an N350 wave with a markedly smaller amplitude also appeared during trials containing no K-complex. Ujszászi and Halász (1988) assumed that the N350 and N550 are not functionally connected with each other but instead represent parallel processes. This view was mainly based on their findings (Ujszászi & Halász, 1986) showing that the latency of the prevalent negative wave varies within subjects, as well as between single responses. At times the N350 wave is predominant and at times the N550 wave dominates. Ujzsászi and Halász (1986) suggested that the N350 wave is more of a reflection of stimulus processing, while the N550 is more associated with "the sleep state dependent processes". Harsh (1994) focused on the function of N350 but not on that of the later complex because his main interest was in the sleep onset process during which no N550-P900 complex occurs. He hypothesised that the N350 reflects the activation of a mechanism whose function is to inhibit the processing of stimulus information or the initiation of an overt response to a stimulus while a person is falling asleep. This hypothesis is mainly based on the findings that the N350 appears at the same time with the attenuation of the P3b and the impairment of behavioural responsiveness in the sleep onset process (Harsh et al., 1994) and, further, that the N350 is elicited also by task-irrelevant and repetitive stimuli (Williams et al., 1962).

For the last 30 years, a debate on the nature and functional significance of the K-complex has been in progress. The dispute concerning the nature of the K-complex has concentrated on the question of whether the K-complex is an all-or-none phenomenon. Results favouring the affirmative answer have shown that the K-complex is not systematically affected by the manipulation of various stimulus parameters when a stimulus succeeds in eliciting a K-complex (Bastien & Campbell, 1992; Roth et al., 1956). Ujszászi and Halász (1986) reached the opposite conclusion. They found that, although EEG responses to an invariable stimulus greatly varied in amplitude, the same components could be found for small and large amplitude responses. Usually only the latter are considered K-complexes. Ujszászi and Halász (1986) suggested that the small and large amplitude responses do not form separate response categories but that they form a continuum.

The two contrary hypotheses on the functional significance of the K-complex have been that the K-complex either i) facilitates the response to

external events, in that it acts as an OR, or ii) reduces the sensitivity of the sleeping brain to external stimuli by acting as a DR. The evidence for the orienting hypothesis of the K-complex mainly arises from results showing that i) sensory stimulation increases the frequency of the K-complex (Halász et al., 1985) and ii) the K-complex is often accompanied by clear signs of arousal elevation (Roth et al., 1956). The DR hypothesis in turn is based on both EEG and HR data. The main findings favouring this hypothesis are that i) the K-complex resembles slow wave activity (Loomis et al., 1939); ii) stimuli that lead to complete awakening do not elicit a K-complex (Koella, 1967); iii) the number of K-complexes is lower in patients with a sleep disorder than in normal controls (Wauquier, Aloe, & Declerck, 1994); and iv) the K-complex is associated with an accelerative HR response (Berg et al., 1975; Church, Johnson, & Seales, 1978; Keefe, Johnson, & Hunter, 1971). This last piece of evidence is based on Graham's hypothesis that the accelerative HR response represents a cardiac component of the DR (Graham, 1979; Graham & Clifton, 1966).

1.3 Variability of responsiveness during sleep

The afore-mentioned studies with different measures of stimulus processing demonstrate that variability is a fundamental characteristic of responsiveness to external stimuli during sleep (see Section 1.1). For example, instructed behavioural responses, recalling of the presented stimulus after awakening, and incorporation of stimuli into dream content do not occur during each trial, but only occasionally. The stimuli used in these studies have, however, been so distinctive that their perception would probably be easy in wakefulness. This increased variability of responsiveness commences even before sleep in sleepiness (for a review, see Dinges & Kribbs, 1991).

In spite of this obvious unevenness in the responsiveness to external stimuli within a single sleep stage, sleep ERP studies have mainly focused on the effects of sleep stages and the manipulation of various stimulus parameters on ERP waves, which are, of course, important factors as well. It would, however, be essential to know also whether some processes can be activated more easily under certain conditions within a single sleep stage. An essential question in this context is which physiological events indicate the sleeping brain's responsiveness to external stimuli. In NREM sleep, a potential marker is the K-complex. As mentioned in Section 1.2.2.3, the K-complex does not usually occur to an invariable stimulus in each trial. Ujszászi and Halász (1986) have concluded that the elicitation of the K-complex may indicate improved possibilities for stimulus processing. This interpretation agrees with the hypothesis of Niiyama et al. (1995) that the cognitive processing of stimuli is augmented when the stimulus elicits a K-complex. The authors found that the difference in ERPs within the latency range of the K-complex between a standard and deviant stimulus was greater when both stimuli elicited a K-complex than when neither did. They assumed that this difference was due to a slow negative wave reflecting a cognitive process. Halász and Ujszászi (1991)

considered the possibility that the K-complex represents microarousal. All these interpretations of the K-complex suggest that the sleeping brain is in a more open state to a non-awakening external event when the event elicits a K-complex than when it does not.

The K-complex could be a useful tool especially when the occurrence of the MMN response is studied during NREM sleep. It offers an indication of the responsiveness of the brain to the presented stimulus and it does not overlap the latency range of the MMN observed in wakefulness. Of course, it is possible that the MMN latency is markedly longer in sleep than in wakefulness and therefore leads to difficulties in detecting the MMN component if it occurs in association with the elicitation of the K-complex.

As mentioned in Section 1.2.2.3, the K-complex does not occur in REM sleep. EEG in REM sleep is very similar to EEG in wakefulness, and it does not contain phasic events that can be considered indications of increased responsiveness to external stimuli. A promising phasic event is REM. As presented in Section 1.2.2.2, the brain can be considered to be more preoccupied by the ongoing cognitive activity during phasic REM sleep characterised by bursts of REMs than during tonic REM sleep characterised by the absence of REMs. In addition, behavioural responsiveness is at a lower level during phasic than during tonic REM sleep (Price & Kremen, 1981). The possible relationship between the alternation of phasic and tonic periods of REM sleep and the occurrence of the P3b to external stimuli during REM sleep would be of interest because the attentional state has been shown to affect the elicitation of the P3b in wakefulness (see Section 1.2.2.2). Thus the appearance of the P3b in response to external stimuli should occur more likely during tonic than phasic REM sleep.

2 OBJECTIVES OF THE STUDY

The general objective of the present study was to investigate the processing of physical changes in a repetitive auditory stimulus stream during sleep and sleepiness with ERPs in young human adults. In the case of sleep, the starting point was the fact that cortical preparedness for the processing of physical stimulus changes considerably varies from moment to moment even within a single sleep stage, and it is essential to take this fluctuation into account prior to the averaging of ERPs. In this context, NREM stage 2 and REM sleep become the most interesting stages because there are useful markers for the fluctuation. K-complexes and REMs were used as markers of the fluctuation in NREM stage 2 and REM sleep, respectively. Sleepiness was included so that it could be determined whether the attenuation of the highly automatic processing of external events characteristic of sleep commences already during the state immediately preceding sleep. Thus the present study covered the entire spectrum of reduced alertness from sleepiness to NREM and REM sleep, with the exception that SWS was not included.

The present study was composed of three different series of experiments which allowed one to examine different problems. In Study I, the focus was on the occurrence of the MMN response during NREM stage 2 sleep. The aim was to determine whether a MMN response is more likely to occur when a deviant stimulus produces a K-complex than when it does not during stage 2 sleep. This objective was based on interpretations favouring the view that the sleeping brain is more open to external events when a stimulus elicits a K-complex than when it does not (see Section 1.4).

Study II was designed to replicate the results of Study I. An additional objective was to determine other precursors of the evoked K-complex in ERPs in addition to the MMN-like deflection. It was expected that the increased responsiveness of the brain to external events, as reflected in the elicitation of the K-complex to a deviant tone, is present even for some time prior to the eliciting stimulus. This expectation was based on Pál et al.'s study in which single responses to the same sound could be classified into K-complex and no K-complex categories with a high probability on the basis of the prestimulus EEG (see Section 1.2.2.3).

The objective of Study III was to determine the differences in ERPs to pitch changes between the tonic and phasic periods of REM sleep. The aim was especially to determine whether a P3b-type wave occurs more likely during tonic than phasic REM sleep. This question arose from studies suggesting that i) the brain is more preoccupied with ongoing mental activity and ii) behavioural responsiveness is at a lower level during phasic REM sleep than during tonic REM sleep (see Section 1.2.2.2).

Study IV investigated whether the MMN and also P3 responses are attenuated already during sleepiness before sleep. An attempt was made to overcome the shortcomings of the previous studies (see Section 1.2.2.1). The present study differed from the previous ones in the following three essential respects: in the present study i) optimal stimulus conditions were used for the recording of the MMN component, ii) both objective and subjective measures of sleepiness were used, and iii) performance in a reaction time task was measured simultaneously with the recording of the MMN component.

3 STUDY I

Is the appearance of mismatch negativity during stage 2 sleep related to the elicitation of K-complex?

3.1 Introduction

Earlier studies have failed to show convincingly the occurrence of the MMN response during NREM sleep in young adult humans (Loewy et al., 1996; Nielsen-Bohlman et al., 1991; Paavilainen et al., 1987; Winter et al., 1995). It is, however, possible that the occurrence of the MMN response is associated with the fluctuation of responsiveness to external stimuli during NREM sleep. A possible indication of this fluctuation is the elicitation of a K-complex to a stimulus. The occurrence of the K-complex has been considered to indicate an increased openness of the brain to external stimuli (Niiyama et al., 1995; Ujzsászi & Halász, 1986).

In the present study, single EEG responses to a deviant tone were classified as a K-complex (KC), another phasic EEG event (OPE), or no response (NR) prior to the averaging of the ERPs. The hypothesis was that the occurrence of the MMN response during NREM sleep would be more likely during the KC than during the OPE or NR trials. The study was limited to stage 2 sleep because the classification of trials is difficult in SWS due to large amplitude, spontaneous delta activity. Two kinds of stimulus paradigms were employed, the oddball paradigm (infrequent deviant tones presented among frequent standard tones) and the OR paradigm (infrequent tones presented without intervening standard tones). The OR paradigm was employed to determine whether a possible MMN-like deflection in the oddball situation is a genuine MMN response. If it were true MMN, it should not appear in the OR situation because of the absence of the memory trace for the standard tone with which the input of the deviant tone could be compared.

3.2 Methods

Subjects
Ten healthy volunteers (5 men and 5 women) 16-33 years of age and without self-perceived hearing problems participated in an experiment containing two nights in the laboratory. The subjects were instructed to refrain from the use of alcohol for 24 h before the experiment.

Procedure and stimuli
During the experimental night, the stimuli were presented according to either the oddball paradigm or the OR paradigm. The order of the paradigms was balanced across the subjects. The stimuli were presented via a loudspeaker that was placed behind the lying subjects' head. ERPs were recorded during a reading session and a whole night's sleep.

The stimuli of the oddball paradigm contained an infrequent deviant tone of 1200 Hz and a frequent standard tone of 1000 Hz. The probabilities of these tones were 2% and 97.5%, respectively. Both stimuli were 45 dB tone (measured from the pillow) bursts of 50 ms duration with a rise/fall time of 10 ms. The constant ISI was 625 ms. The subjects were also presented speech stimuli at the probability of 0.5%, but this part of the experiment goes beyond the focus of the present study. The interval between two consecutive deviant stimuli varied between 20 and 45 s. In the OR paradigm, the deviant stimuli (hereafter called OR stimuli) were presented in the same manner as the deviant tone in the oddball paradigm.

Recordings
ERPs were measured from Fz, Cz, Pz, and M2 (right mastoid) channels referenced to the nose. EEG epochs of 1500 ms before and after the deviant/OR tone were digitised at the sampling rate of 200 Hz. The time constant and low-pass filter were 1 s and 100 Hz, respectively. Separate data were collected for off-line visual sleep stage scoring. They contained EEG, electro-oculographic (EOG), and electromyographic (EMG) epochs digitised at 100, 50, and 200 Hz sampling rates, respectively. The saving period was 10 s before and after the deviant tone. The electrodes were placed and sleep stages were scored according to the criteria of Rechtschaffen and Kales (1968).

ERP analysis
The single trials were classified into the KC, OPE, and NR categories on the basis of responses to the deviant tone. The criteria for a KC response were that the morphology and duration had to meet the standards set by Rechtshaffen and Kales (1968) and its amplitude had to exceed 75 μV either at Fz or Cz. A trial was considered an OPE when the post-deviant stimulus EEG showed a clear phasic event that deviated from the pre-deviant stimulus EEG but did not meet all the criteria of the KC response. A trial that contained no discernible phasic event in the post-deviant tone EEG was classified an NR. A visible phasic event (KC or OPE) had to emerge within the latency range of 200-1000

ms to be considered stimulus-elicited. The corresponding classification was applied for the data from the OR paradigm. In addition, trials containing either a maximum peak-to-peak amplitude over 75 μV or a sleep spindle (or both) within a latency of 0-200 ms after the deviant/OR stimulus onset were excluded to improve the signal-to-noise ratio in this critical window.

The MMN was identified from a deviant minus standard tone difference wave. An analysis of variance (ANOVA) was used to test whether the negative peak amplitude in the ERPs to the deviant tone significantly ($p<.05$) differed from the corresponding value in the ERPs to the standard tone. The focus was in the latency range of 100-250 ms. An ANOVA was performed when the difference curve showed a clear negative deflection within this latency range.

3.3 Results

Oddball paradigm

The data of six subjects who had a sufficient number of all trial types (>20 each) during stage 2 sleep were subjected to the statistical analyses. The data of the M2 channel was excluded from the statistical analysis due to a poor signal-to-noise ratio.

MMN during reading. A clear negative wave could be observed within the MMN latency range at Fz ($F(1,5)=13.3$, $p<.05$), Cz ($F=18.5$, $p<.01$), and Pz ($F=14.5$, $p<.05$). The typical inversion of the MMN polarity at M2 was not observable, probably because of the poor signal-to-noise ratio at this channel.

Distribution of the probabilities of the KC, OPE, and NR trials. The deviant tone was followed on average by a KC, OPE, and NR event with probabilities of 22.2, 23.5, and 54.3%, respectively. The corresponding probabilities for the standard tone were 1.8, 23.3, and 74.9%. The probability of the KC events was significantly higher for the deviant than for the standard tone ($t(5)=8.22$, $p<.001$). The situation was the opposite for the NR events ($t(5)=-3.16$, $p<.05$). No difference was found for the OPE events.

MMN during stage 2 sleep. When the ERPs were averaged across all (KC, OPE, and NR) the trials, no MMN-like wave could be detected. Only K-complex deflections (N350, N550, and P900) and a P250 wave were identified.

MMN during the KC trials. An MMN-like deflection was observed within the MMN latency range preceding the P250 wave and K-complex deflections (Fig. 1). This deflection was significant at Fz ($F(1,5)=7.0$, $p<.05$) and Cz ($F=26.6$, $p<.01$). The maximum peak amplitude occurred at Fz (-7.67 μV). Similarly to the waking MMN, the polarity inversion of the MMN-like deflection could not be observed. The peak latency seemed to be shorter for the MMN-like deflection (140 ms) than for the waking MMN (200 ms), but the difference failed to reach significance.

MMN during the OPE trials. No MMN-like deflection could be identified during the OPE trials (Fig. 2). The ERPs contained the P250 wave and K-complex deflections. The latter waves were of smaller amplitude than during the KC trials.

MMN during the NR trials. The ERPs revealed no sign of the MMN-like deflection during the NR trials (Fig. 3). Only a P250 wave was observed.

OR paradigm

Eight subjects had a sufficient number of all trial types (>20 each) for the ERPs. The distribution of the probabilities of the KC, OPE, and NR trials were 35.2, 34.2, and 30.6%, respectively.

ERPs during reading. The ERPs showed an N1 wave at all the midline channels (Fz: $F(1,7)=28.0$, $p<.01$, Cz: $F=34.1$, $p<.01$, Pz: $F=24.7$, $p<.01$) but no MMN to the OR stimulus during the reading session. The N1 was followed by two positive waves, of which the latter reached significance for all the channels (Fz: $F(1,7)=7.6$, $p<.05$, Cz: $F=7.6$, $p<.05$, Pz: $F=8.5$, $p<.05$, M2: $F=13.9$, $p<.01$).

MMN-like deflection during the KC, OPE, and NR trials. No MMN-like deflection was detected for the OR stimulus during any trial type (Fig. 4). Interestingly, the N1 wave was not present even during the KC trials. Otherwise the ERPs of the various classes were comparable with those observed in the oddball paradigm.

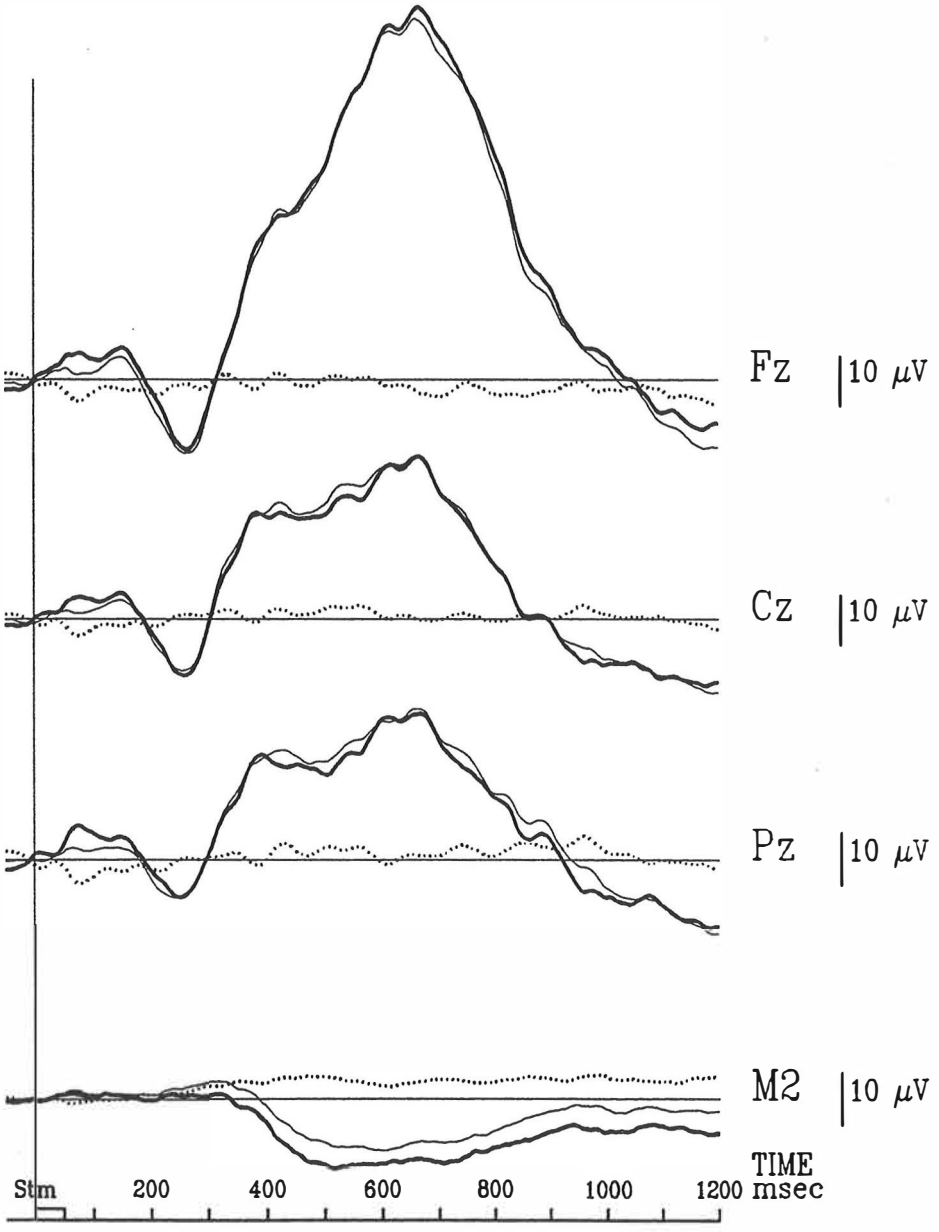

FIGURE 1 Grand-average ERPs (N=6, 207 trials) to the standard (dotted line) and deviant (thin line) stimuli during the KC trials of stage 2 sleep. The difference waveforms of the grand-average ERPs (thick lines) are derived by subtracting the ERPs to the standard tones from the ERPs to the deviant tone. Negativity up.

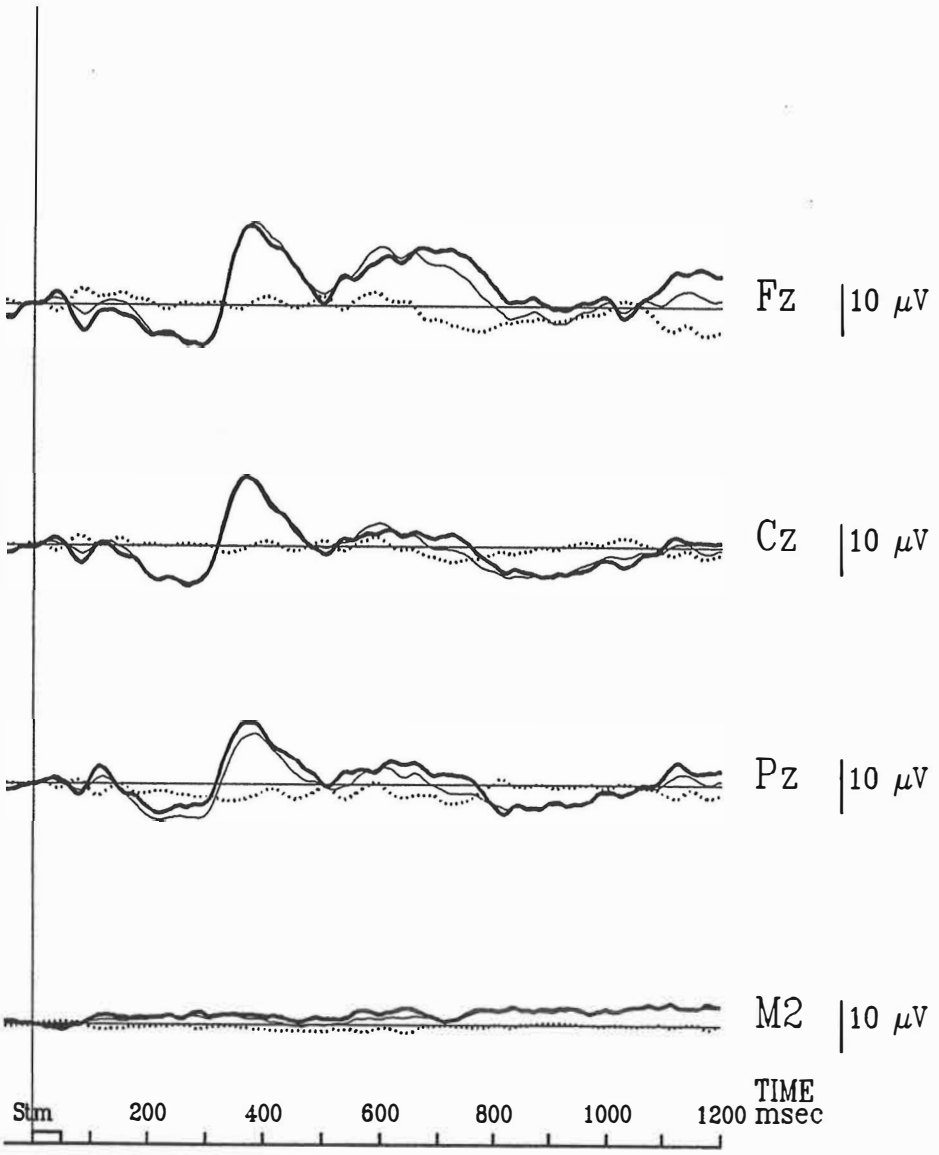

FIGURE 2 Grand-average ERPs (N=6, 219 trials) to the standard (dotted line) and deviant (thin line) stimuli during the OPE trials of stage 2 sleep. The difference waveforms are shown with thick lines. Negativity up.

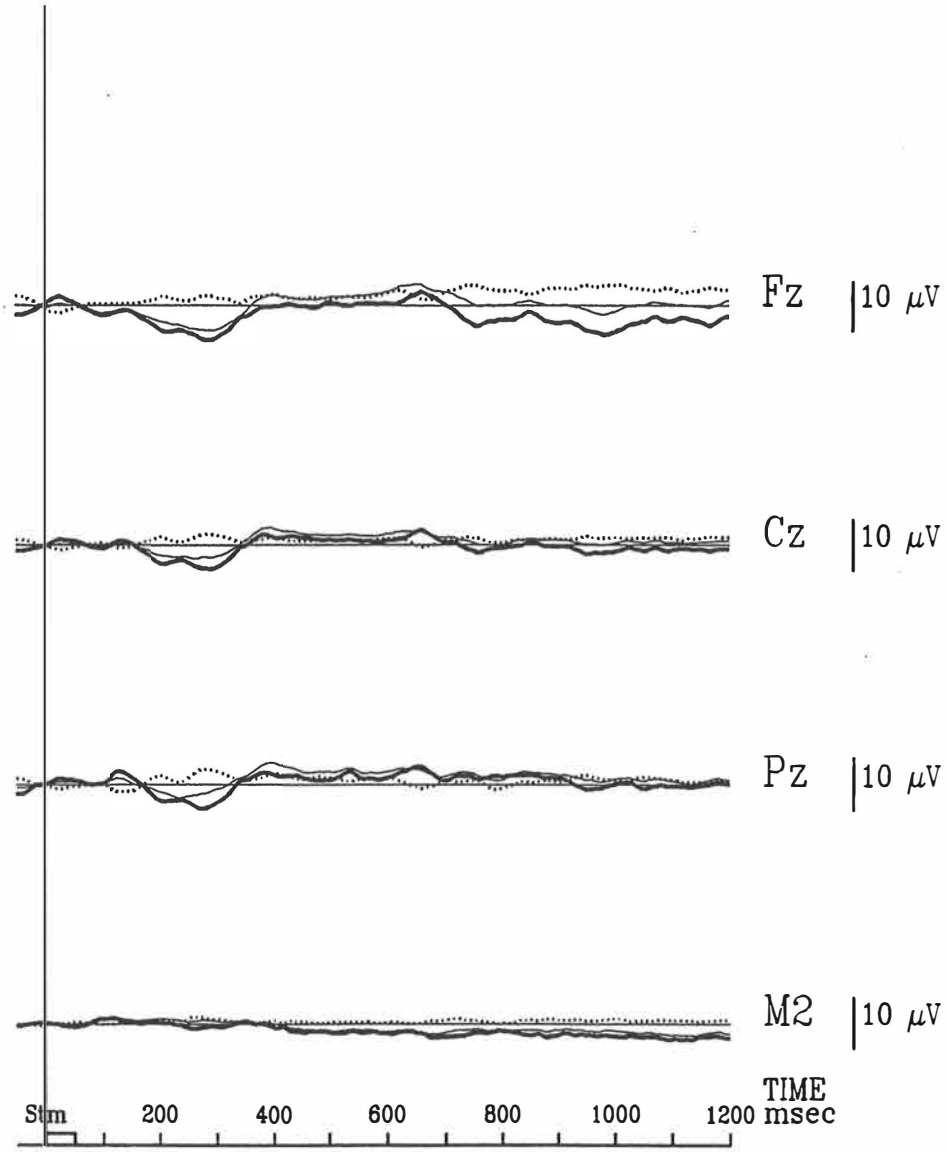

FIGURE 3 Grand-average ERPs (N=6, 507 trials) to the standard (dotted line) and deviant (thin line) stimuli during the NR trials of stage 2 sleep. The difference waveforms are shown with thick lines. Negativity up.

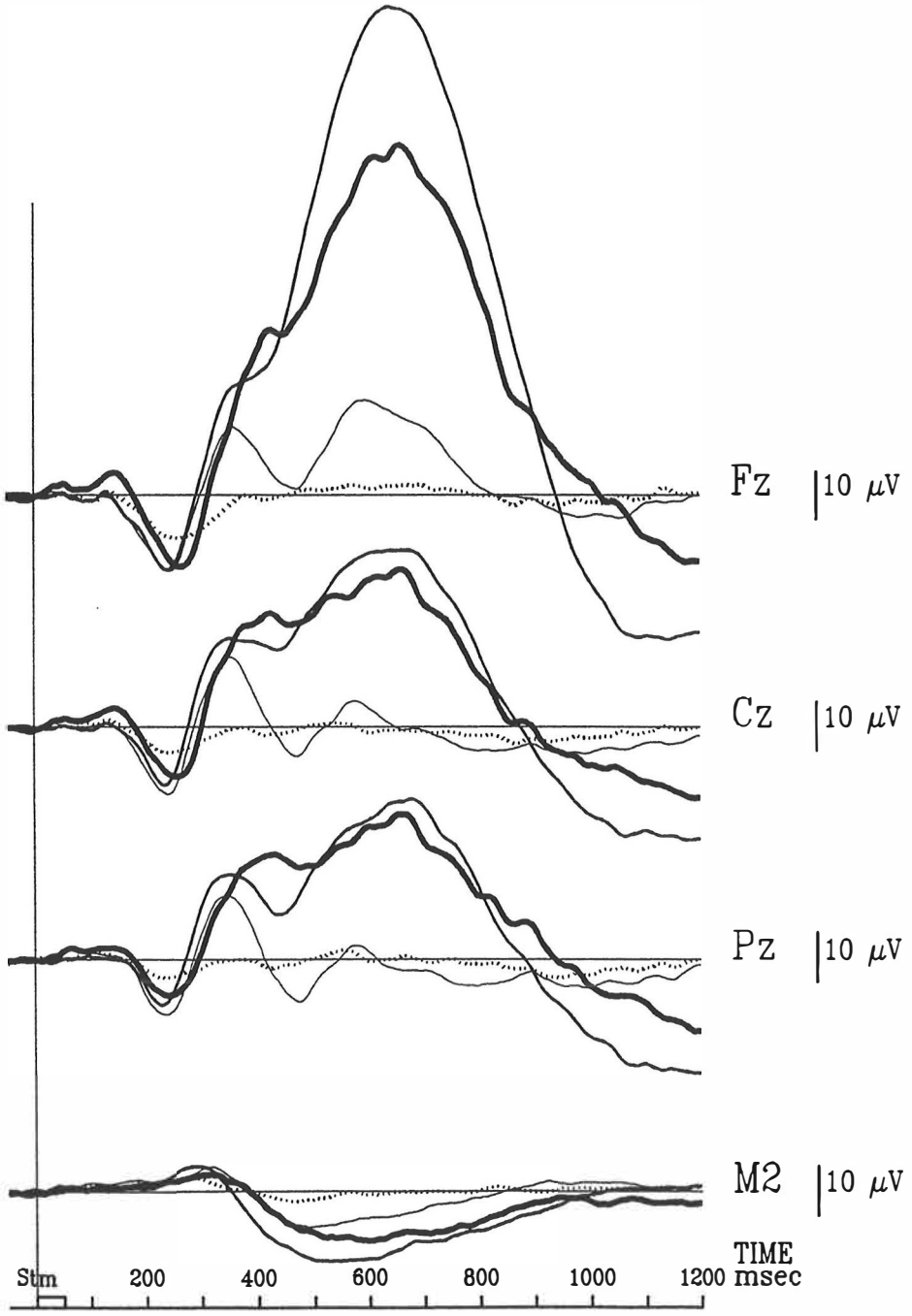

FIGURE 4 Grand-average ERPs to the tones presented without the standard tones (OR paradigm) during the KC (the second thickest line, 543 trials), OPE (thin line, 528 trials), and NR (dotted line, 472 trials) trials. The thickest line shows the grand-average ERPs to the deviant tones presented with the standard tones during the KC trials (207 trials). Negativity up.

3.4 Discussion

The results of this study support the hypothesis that the occurrence of the MMN response during stage 2 sleep is positively associated with the elicitation of the K-complex in response to a stimulus change. The main findings supporting this hypothesis were the occurrence of the MMN-like deflection only during the KC trials in the oddball paradigm and the disappearance of this response after the removal of the standard tones around the deviant tones (the OR paradigm). Thus the MMN-like deflection acted to the removal of the standard tones in the same manner as the waking MMN in the present and previous studies (Näätänen et al., 1989; Sams et al., 1985a).

A finding of interest was that no N1 wave could be observed for the OR stimulus even during the KC trials in stage 2 sleep but the MMN-like deflection was detected for the deviant tone. The attenuation of the N1 wave in sleep is a well-known phenomenon (Bastuji et al., 1995; Campbell et al., 1988; Nielsen-Bohlman et al. 1991; Paavilainen et al., 1987; Winter et al., 1995). Thus, on the basis of these results, the MMN response seems to be elicited more easily than the N1 during KC trials. The N1 is, however, thought to represent a more primary form of stimulus processing than the MMN. Thus the absence of the N1 wave to the OR stimulus during the KC trials can be considered somewhat confusing if the MMN-like deflection to the deviant stimulus represented genuine MMN. Paavilainen et al. (1987) concluded that the disappearance of the MMN component during sleep in their study was not surprising because no N1 wave occurred.

Other findings that do not support the view that the MMN-like deflection represented genuine MMN are its unusually early onset and peak latency. It would be more logical for stimulus processing to take more time in sleep than in wakefulness.

Finally, the statistical power of the current data was poor because of the small number of subjects and trials. Thus it is possible that the MMN-like deflection was due to chance. More evidence must be presented before the occurrence of the MMN response during KC trials of stage 2 sleep can be established.

Concluding remarks

The present study suggests that a MMN response may be possible during stage 2 sleep, but its demonstration requires that the fluctuation of microstates of sleep be taken into consideration. Further studies are, however, needed to confirm this result.

4 STUDY II

Precursors of the evoked K-complex in event-related brain potentials in stage 2 sleep

4.1 Introduction

The recent view of sleep is that it is not only composed of traditional sleep stages (Rechtschaffen & Kales, 1968), but that there is a continuous fluctuation of microstates that differ in terms of responsiveness to external stimuli (Ujszászi & Halász, 1986). An essential characteristic of stage 2 sleep is that a stimulus elicits a K-complex, but not in all trials. Therefore the question arises of whether EEG events that precede K-complex and no K-complex responses also differ. Previous studies have shown an enhancement of an ERP component called N350 in conjunction with the elicitation of a K-complex (Bastien & Campbell, 1992; Niiyama et al., 1995). Study I showed that an ERP component labelled mismatch negativity (MMN) may also occur to a stimulus change in this same situation. These findings suggest that a stimulus is processed differentially prior to the onset latency of the K-complex between trials containing a K-complex (KC trials) and those containing no K-complex (NO KC trials) immediately after the stimulus. Interestingly, this differential processing in association with the elicitation of the K-complex may be present even before a stimulus to which a K-complex occurs. Pál et al. (1985) showed that the elicitation of the K-complex to a stimulus depends on the brain state immediately before the stimulus is presented. The authors correctly classified 89% of the single responses into K-complex and no K-complex categories on the basis of the pre-stimulus EEG power spectra.

One objective of the present study was to replicate the previous findings of an enhancement of the N350 wave and the occurrence of the MMN-like deflection during KC trials. Secondly, the association between the P210 wave and the elicitation of the K-complex was examined. In previous studies, this association has not been in the focus. Three responses (MMN, P210, N350) to

pitch-deviant tones presented among homogeneous standard tones were measured. Thirdly, possible differences in the ERPs to the standard tones in association with the elicitation of a K-complex to the immediately following deviant tone were examined. It was expected that the ERPs to the standard stimuli would indicate an increased responsiveness when the following deviant stimulus elicits a K-complex. In addition, it was examined whether the ERPs to the preceding standard tones differed between trials containing a K-complex to a small stimulus change and trials containing a K-complex to a large stimulus change. It can be expected that, on average, the more sensitive the sleeping brain to external stimuli, the weaker the stimulus that succeeds to elicit a K-complex. This difference in sensitivity is probably present for some time prior to a stimulus to which a K-complex occurs (Pàl et al., 1985).

4.2 Methods

Subjects
Fifteen healthy volunteers (8 women and 7 men, aged 19-35 years) participated in an experiment containing two nights in the laboratory. The use of alcohol was forbidden for 24 h prior to the experiment.

Procedure and stimuli
Two different data sets were collected during the nights in the laboratory (one type of data per night). The data shown in this report were obtained during the first night in seven cases and during the second night in the laboratory in eight cases.

The presentation of stimuli occurred in the same manner as in Study I. The stimuli used contained a frequent standard stimulus of 1000 Hz (p=97%) and infrequent small and large deviant stimuli of 1100 and 2000 Hz (p=1.5% for each), respectively. The other stimulus parameters were the same as in Study I, except that intensity was 50 dB (measured from the pillow).

Recordings
Both the ERP data and the data for sleep stage scoring were collected in the same manner as in Study I, with the exception that the M2 channel was not included.

ERP analysis
Trials with EMG artefacts were excluded using the same criteria as in Study I. No trials with eye movements were found during stage 2 sleep.

The ERP trials that contained two pre- and two post-deviant tone standards in addition to a deviant tone were classified into K-complex (KC) and no K-complex (NO KC) categories on the basis of the responses to the *deviant* tones. The criteria of the KC category were the same as in Study I. The OPE and NR categories used in Study I were now combined into a NO KC

class. The large deviant tone elicited 1553 KC and 1779 NO KC responses. The corresponding numbers were 414 and 3243 for the small deviant tone. The pre-deviant epoch of 1500 ms contained 375 K-complexes in 6989 trials.

The ERP scores for the MMN-like (50-200 ms), P210 (150-300), and N350 (300-400 ms) deflections were baseline-corrected mean microvolt values that were calculated for each 50 ms slice of response windows. In the case of the MMN response, the scores were calculated from the deviant minus standard difference waves.

Statistical analysis

The occurrence of the MMN-like deflection was tested with a multivariate analysis of variance (MANOVA) (Fz, Cz and Pz channels as dependent variables) and ANOVA (each channel separately as a dependent variable). The association between the elicitation of the K-complex and the N350 amplitude was tested with a three-way ANOVA with repeated measures on Trial type (KC, NO KC), Deviance (large, small), and Channel (Fz, Cz, Pz). The difference in the ERPs to the standard stimuli between the KC and NO KC trials was tested with a three-way ANOVA with repeated measures on Trial type (KC, NO KC), the following deviance (large, small), and Channel (Fz, Cz, Pz). The significance level was set at $p<.05$. The Greenhouse-Geisser correction was used when appropriate.

4.3 Results

MMN-like deflection

No reliable MMN-like deflection occurred during either the KC or the NO KC trials. The result was the same for both stimulus changes. An MMN-like deflection could, however, be observed especially for the small deviant tone during the KC trials.

In order to improve the signal-to-noise ratio, a further analysis was carried out. It contained data from six subjects with a high number (at least 30) of both response types. A significant MMN-like wave was observed for the small deviant tone at Fz *($F(1,5)=42.7$, $p<.01$)* during the KC trials (Fig. 5). A corresponding response was not found for the large deviant tone. During the NO KC trials, no reliable MMN-like wave occurred.

P210 wave

The ERPs showed a P210 wave in both conditions, and it occurred to both pitch changes (Figs. 6.1 & 6.2). The main effect of the Trial type was not significant. The Trial type × Deviance interaction was, however, significant *($F(1,14)=5.49$-4.69, $p<.05$)*. In other words, the effect of the Trial type was related to the magnitude of the pitch change. The P210 to the large deviance was larger during the KC than NO KC trials *($F(1,14)=19.62$, $p<.01$)*. No corresponding effect could be found for the small deviance.

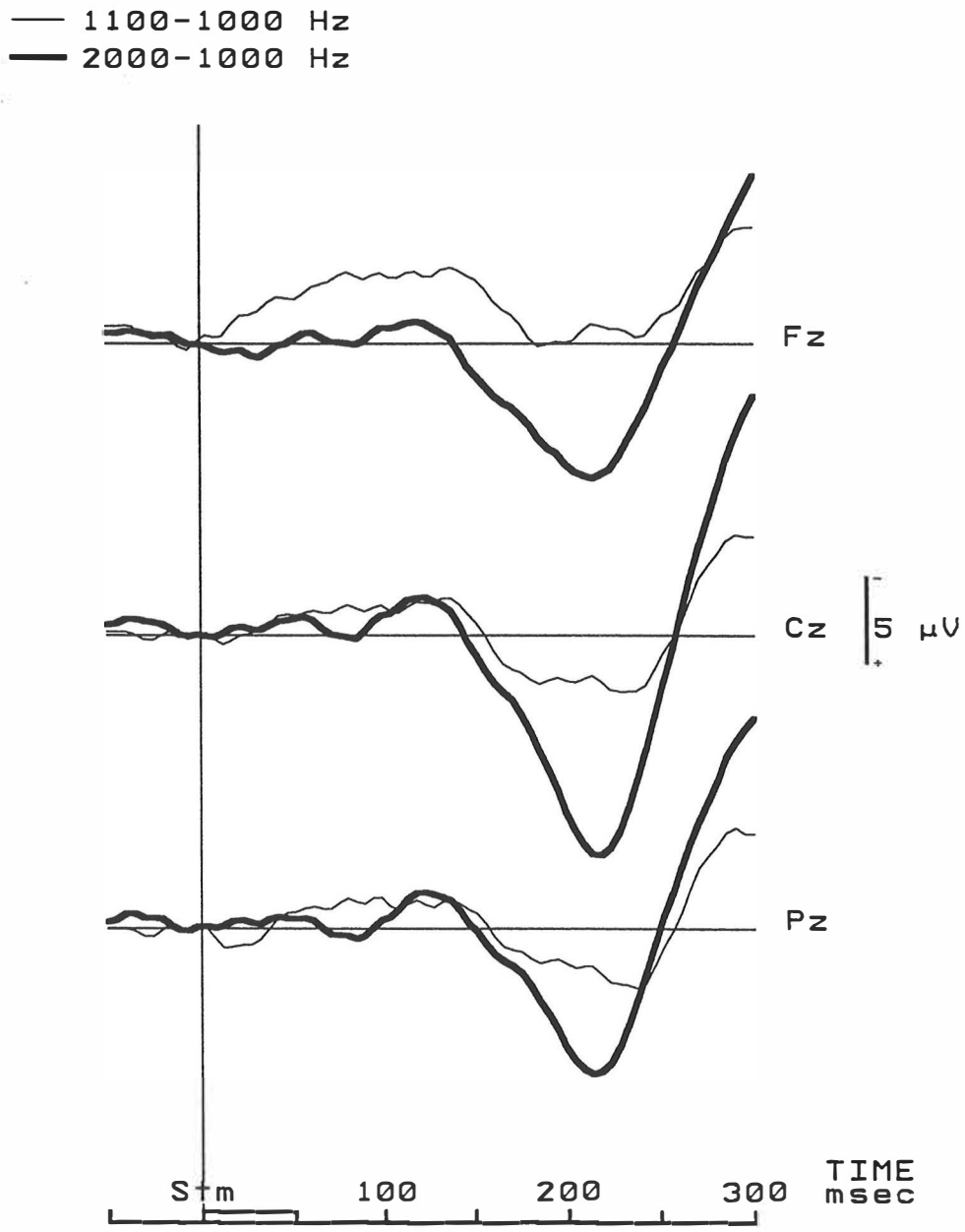

FIGURE 5 Grand-average difference waveforms (N=6) derived by subtracting the ERPs to the standard tones from the ERPs to the *small* deviant tones (thin line, 241 trials) and from the ERPs to the *large* deviant tones (thick line, 599 trials) during the KC trials. The subjects who had at least 30 KC and NO KC trials for each deviant tone are included.

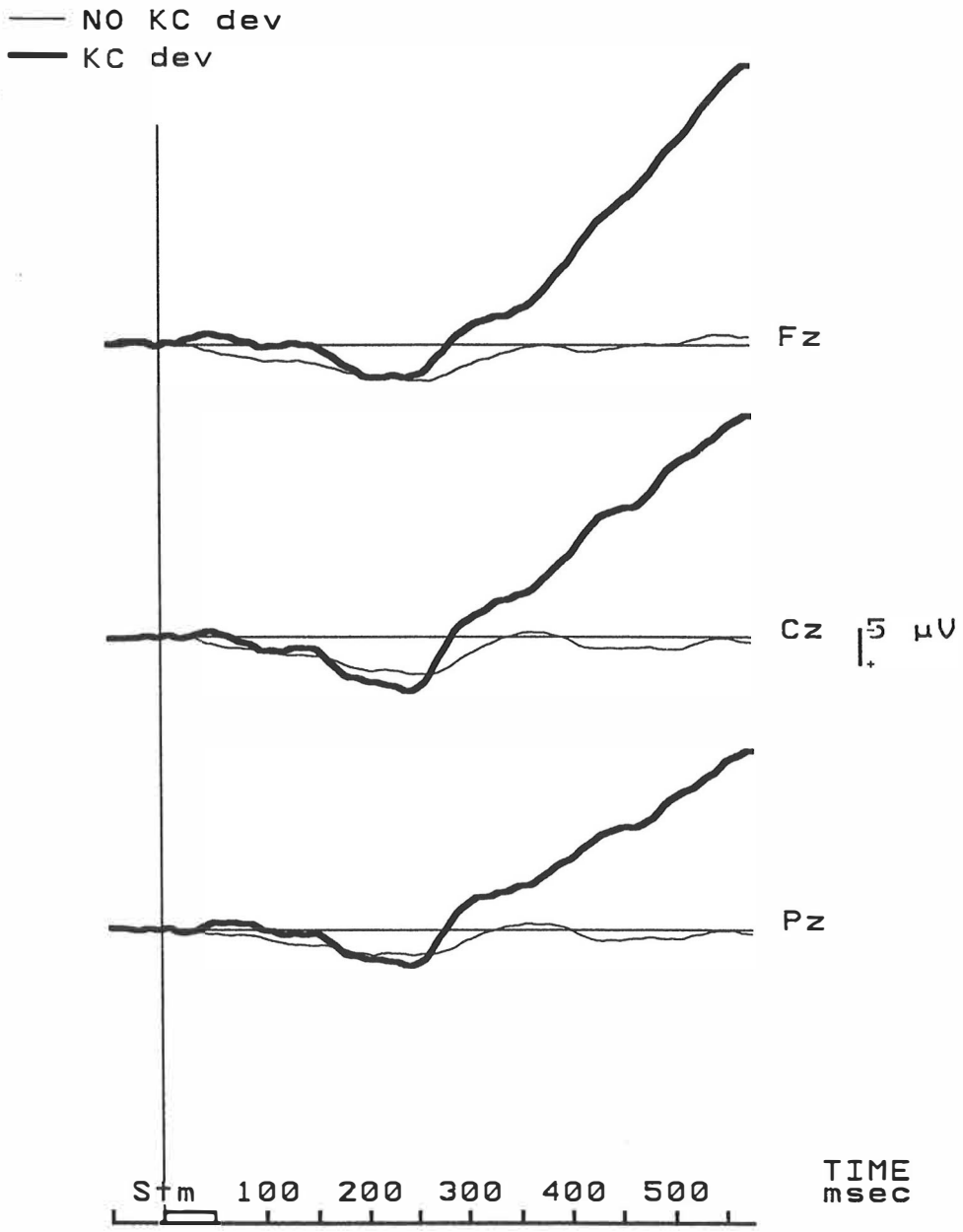

FIGURE 6.1 Grand-average ERPs (N=15) to the *small* deviant tone during the KC (thick line, 414 trials) and NO KC (thin line, 3243 trials) trials.

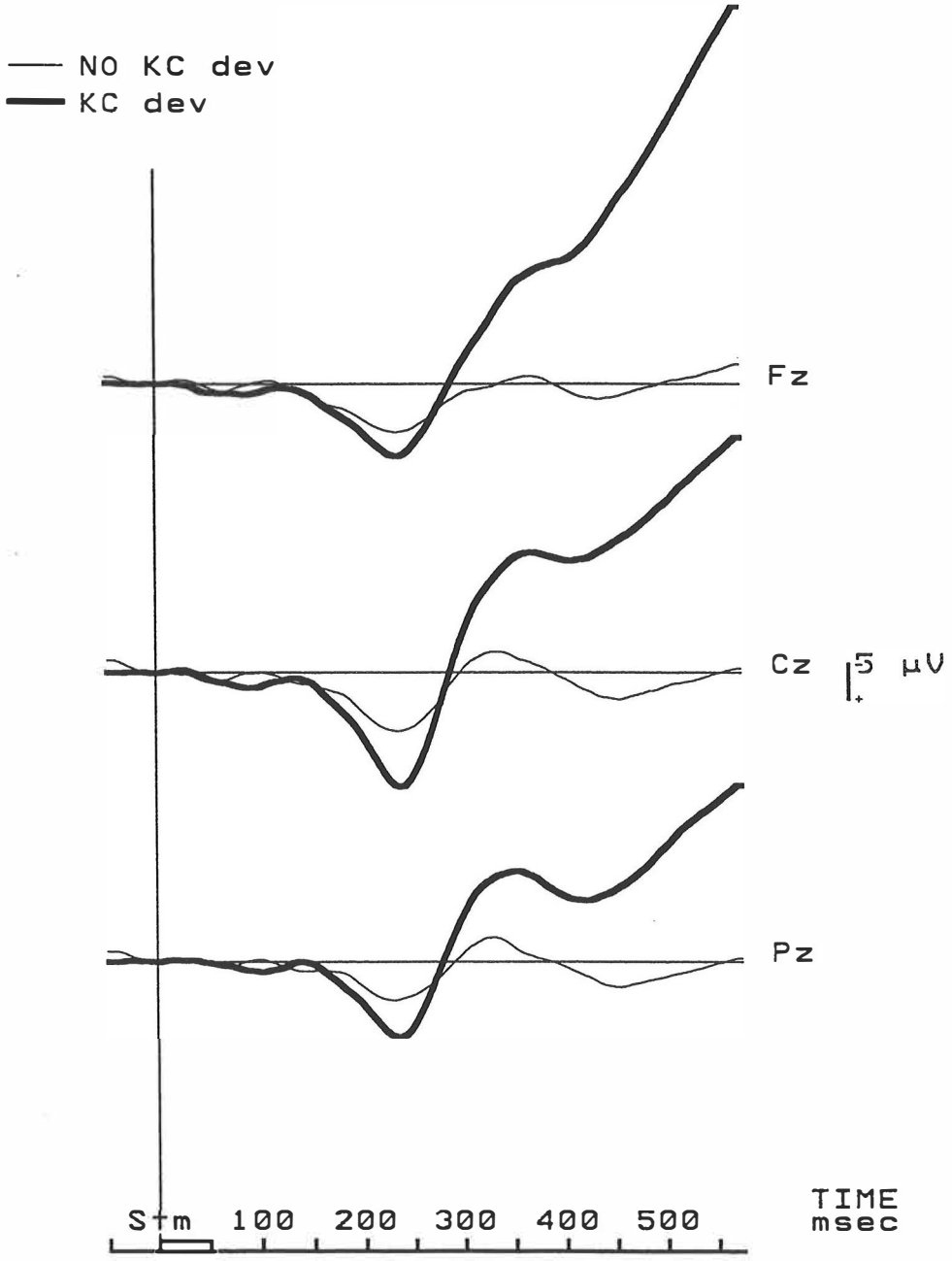

FIGURE 6.2 Grand-average ERPs (N=15) to the *large* deviant tone during the KC (thick line, 1553 trials) and NO KC (thin line, 1799 trials) trials.

N350 wave

The amplitude of the N350 wave was significantly larger during the KC than NO KC trials *(F(1,14)=42.31-42.91, p<.001)* (Figs. 6.1 & 6.2). The N350 wave was almost invisible even for the large deviant tone during the NO KC trials.

ERPs to frequent standard tones

The amplitude of an early positive wave to the standard tone that occurred 625 ms prior to the deviant tone (called the near standard) was larger when the immediately following deviant tone elicited a K-complex than when it did not *(F(1,14)=7.8, p<.05)*. The amplitude or peak latency of the early positive wave was not reliably different in the trials during which a K-complex occurred to the small pitch change, when compared with the large pitch change.

A further analysis with the subgroup of the same six subjects as in the case of the MMN-like wave showed that the amplitude of the early positive wave was higher when the following deviant tone elicited a K-complex than when it did not *(F(1,5)=8.48-8.81, p<.05)* (Figs. 7.1 & 7.2). Again, the ERPs to the near standard tones showed no difference between the KC trials for the small and large pitch change.

No reliable differences in the ERPs to the standard tones that occurred 1250 ms before the deviant tones (called the distant standard) were observed between the KC and NO KC trials. The same result was obtained also when only the six subjects who had at least 30 trials of both response types were included in the analysis (Figs. 8.1 & 8.2).

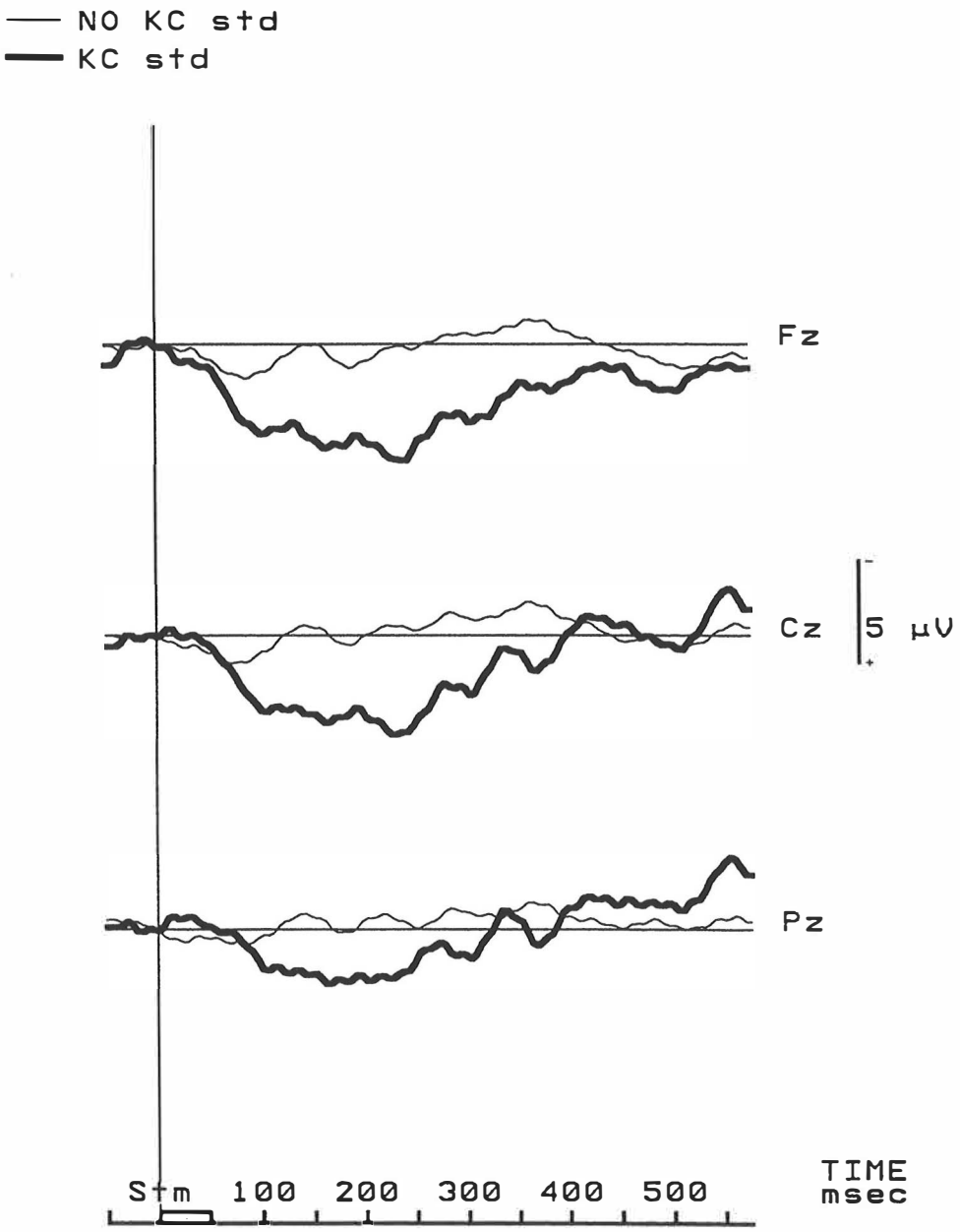

FIGURE 7.1 Grand-average ERPs (N=6) to the *near* standard tone preceding the *small* deviant tone during the KC (thick line, 241 trials) and NO KC trials (thin line, 1396 trials). The subjects who had at least 30 KC and NO KC trials for each deviant tone are included.

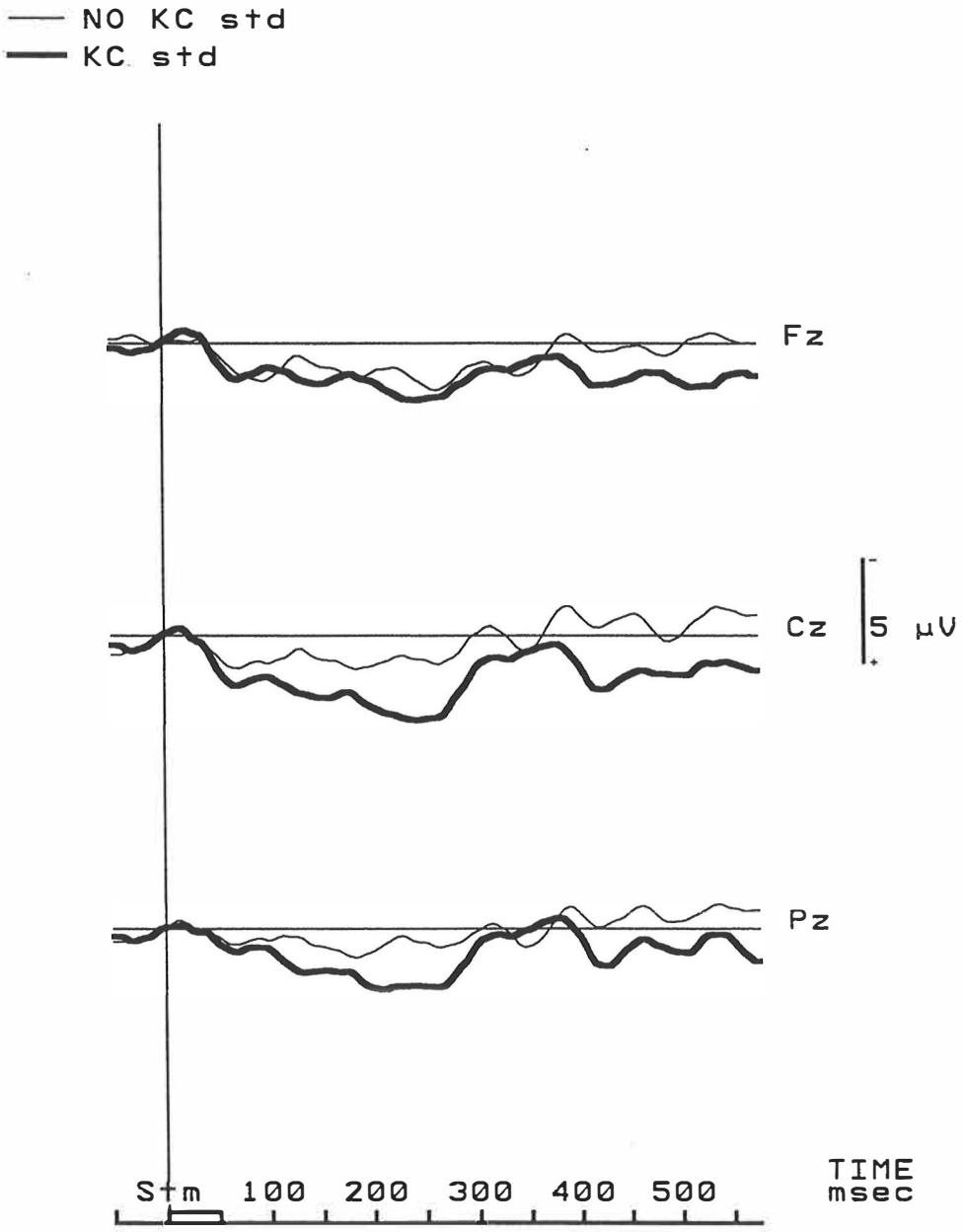

FIGURE 7.2 Grand-average ERPs (N=6) to the *near* standard tone preceding the *large* deviant tone during the KC (thick line, 599 trials) and NO KC (thin line, 823 trials) trials. The subjects who had at least 30 KC and NO KC trials for each deviant tone are included.

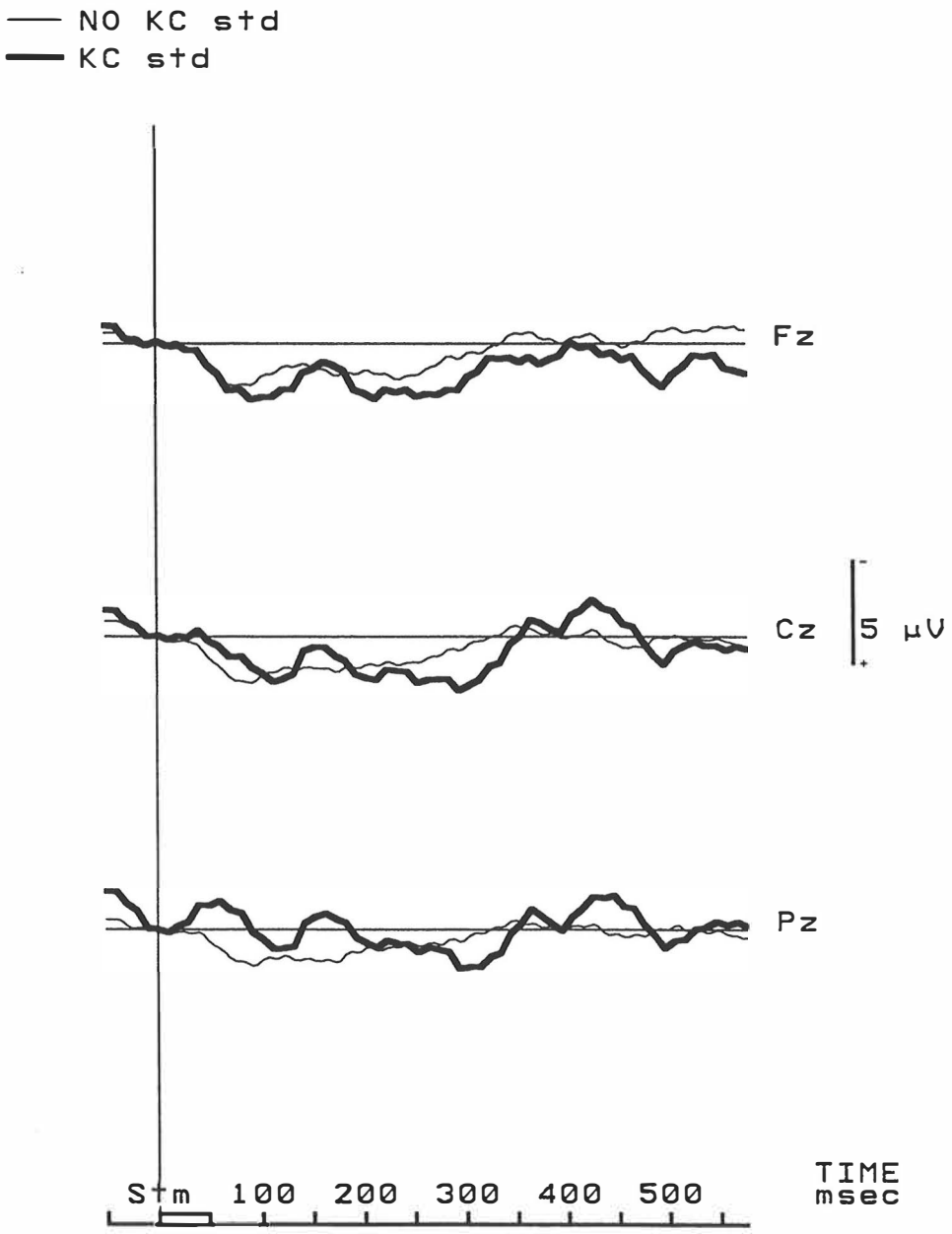

FIGURE 8.1 Grand-average ERPs (N=6) to the *distant* standard tone preceding the *small* deviant tone during the KC (thick line, 241 trials) and NO KC (thin line, 1396 trials) trials.

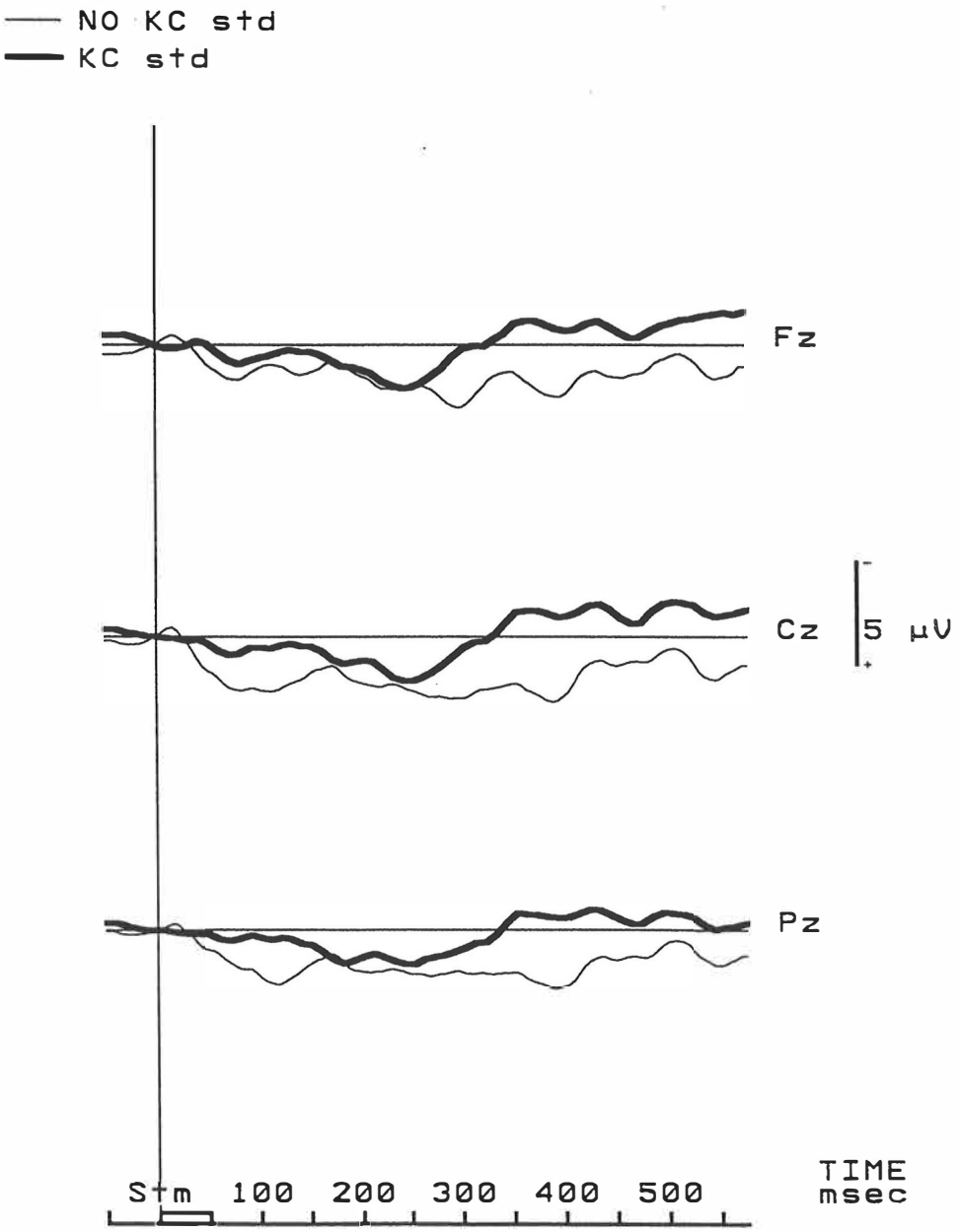

FIGURE 8.2 Grand-average ERPs (N=6) to the *distant* standard tone preceding the *large* deviant tone during the KC (thick line, 599 trials) and NO KC (thin line, 823 trials) trials. The subjects who had at least 30 KC and NO KC trials for each deviant tone are included.

4.4 Discussion

The present study showed that external stimuli are processed differentially prior to the onset latency of the K-complex between trials containing and those not containing a K-complex to deviant tones during stage 2 sleep. This conclusion can be drawn from two results, namely, the ERPs to the deviant tones to which a K-complex occasionally occurred and the ERPs to the standard tones that immediately preceded the deviant tones. The ERPs to the deviant tones differed in the N350 wave that was higher in amplitude during the KC trials. The same held true for the P210 wave to the large deviant tone, but not for the P210 to the small deviant tone. The MMN-like deflection occurred the most reliably for the small deviant tone during the KC trials. The ERPs to the preceding standard tones differed between the trials containing and those not containing a K-complex to the following deviant tone when the distance between the standard tone and the following deviant tone was 625 ms. This difference appeared in an early positive wave that was larger in the case of the elicitation of the K-complex to the following deviant tone. When the distance between the standard tone and the following deviant tone was doubled, no such phenomena could be detected. The ERPs to the standard tones showed no reliable difference in association with the magnitude of the following pitch change.

N350 wave

The enhancement of the N350 wave in association with the elicitation of the K-complex was consistent with the results of Bastien and Campbell (1992). These authors concluded that the N350 may have to reach a certain amplitude before the following N550/P900 complex can occur. Ujszászi and Halász (1988) have presented a different interpretation of the relationship between these two responses. According to these authors, the neural events reflected in the N350 and N550 waves are not functionally connected but, instead, are manifestations of parallel processes. A possible step towards testing Bastien and Campbell's hypothesis would be to determine whether K-complexes exist without the preceding N350 wave. In the present data, the N550/P900 waveform was consistently preceded by a sharp negative wave, but the N350 wave also occurred without a following N550/P900 waveform. Paiva and Rosa (1991) have, however, shown that there are spontaneous K-complexes without preceding negativity. One possibility is that evoked and spontaneous K-complexes differ with regard to the elicitation of the preceding negative deflection. Currently, the reason for the enhancement of the N350 wave in connection with the elicitation of the K-complex is still unknown, however.

The results of the present study showed that the amplitude of the N350 wave was not reliably increased by increasing the magnitude of the stimulus change although this kind of tendency was observed during the NO KC trials (Figs. 6.1 & 6.2). Bastien and Campbell (1992) showed that the N350 amplitude increased as the intensity of a tone increased from 60 dB to 80 dB SPL during the NO KC, but not during the KC trials. The shortening of the rise/fall time

from 20 to 2 ms had, however, no corresponding effect during the NO KC trials. All in all, these results suggest that, during the NO KC trials, the N350 amplitude may be more sensitive to manipulations of the intensity than to manipulations of the rise/fall time or the magnitude of a pitch change.

P210 wave

The results of the present study suggest that the amplitude of the P210 wave is positively associated with the elicitation of the K-complex, but only when the eliciting stimulus clearly changes from its background. This finding supports the view that the P210 wave is less closely associated with the elicitation of the K-complex than the N350 wave is. Thus, contrary to the N350 wave, the P210 wave does not seem to reflect a neuronal activation that would have to reach a certain level of intensity before the N550-P900 waveform can occur. As with the N350 wave, the P210 deflection can not be considered a sufficient condition for the elicitation of the N550-P900 waveform of the K-complex.

MMN-like deflection

The present results partly support the results of Study I on the occurrence of the MMN-like deflection during the KC trials. The more likely appearance of the MMN-like deflection for the small than the large deviant tone was a confusing finding: The increase in the magnitude of the stimulus deviance should have increased rather than decreased the likelihood of the occurrence of the MMN-like deflection. One possible explanation for the failure to record a reliable MMN-like deflection to the large deviant tone during the KC trials may be that it was masked by an overlapping positive wave more effectively than the MMN-like wave to the small deviation. This idea is supported by the finding that the amplitude of the P210 to the large deviant tone was higher during the KC than the NO KC trials. This phenomenon could not be observed for the P210 to the small deviant tone. It is possible that this enhancement of the P210 wave to the large deviant tone in connection with a K-complex was large enough to mask the MMN-like deflection during these trials.

ERPs to frequent standard tones

The finding that the ERPs to the near standard tone preceding the K-complex and no K-complex responses to the immediately following deviant tone are different agrees with the results of Pál et al. (1985). The enhancement of the early positive wave in connection with the evoked K-complex to the following deviant tone suggests that the brain is in a state more responsive to external stimuli for some time before a stimulus to which a K-complex occurs. It is possible that the early positive wave is a P210 deflection with a short onset latency. One reason for this short onset latency could be that there is no overlapping negative wave for the standard tone in contrast to the deviant tone. The finding that the distant standard tone showed no corresponding phenomenon in association with the elicitation of a K-complex to the following deviant tone suggests that responsiveness to external stimuli fluctuates very rapidly during stage 2 sleep.

The fact that the ERPs to the near standard tones showed no reliable difference between trials containing a K-complex to the small or large deviant tone did not support the hypothesis of the study even though a tendency in the expected direction could be observed, especially at Fz (see Figs 7.1 & 7.2). This finding suggests that the brain state is similar when a stimulus elicits a K-complex independently of the physical deviance of the stimulus. The fact that the probability of the elicitation of the K-complex was markedly higher for the large deviant tone (46.6%) than for the small one (11.3%) suggests, however, that a less specific brain state is needed for the elicitation of a K-complex to the large deviant tone than to the small one. It is possible that either the number of stimuli or the number of subjects or both were too small to reveal this expected difference in ERPs to the standard tone during the KC trials.

Concluding remarks

The present study shows that it is possible to find precursors of the evoked K-complex both from the ERP to an infrequent deviant stimulus that occasionally elicits a K-complex and from the ERP to the immediately preceding frequent standard stimulus. The most potential forerunners are the N350 wave to the deviant stimulus and the early positive wave to the preceding standard stimulus. Further studies are needed to confirm the occurrence of the MMN-like deflection in conjunction with the evoked K-complex.

5 STUDY III

Processing of auditory stimuli during tonic and phasic periods of REM sleep as revealed by event-related brain potentials

5.1 Introduction

Previous studies suggest that the brain is more preoccupied by the ongoing mentation during phasic than during tonic REM sleep (Berger & Oswald, 1962; Dement & Wolpert, 1958; Firth & Oswald, 1975; Karacan et al., 1966; Pivik & Foulkes, 1966; Taylor et al., 1985; Weinstein et al., 1988). A question of interest is whether phasic and tonic REM sleep periods also differ in terms of the capacity to process external events. An affirmative answer is supported by Price and Kremen (1980) who found that the behavioural response threshold for auditory stimuli was higher during phasic than tonic REM sleep. The absence of an instructed behavioural response to a stimulus during sleep does not, however, necessarily mean that the stimulus remains undetected because stimuli can be incorporated into a reported dream even when no instructed behavioural response is made to these stimuli (Burton et al., 1988).

One way to clarify the question is to use the ERP method. It provides a direct measure of stimulus-elicited electric changes in brain function. Bastuji et al. (1995) found that a deviant tone, but not a standard tone, elicited an ERP that resembled the P3b during REM sleep. A similar observation was made by Niiyama et al. (1994). This wave (called REM-P3) was not, however, consistently observed in these studies. Bastuji et al. (1995) suggested that this phenomenon resulted from the alternation of the phasic and tonic periods.

The objective of the present study was to examine differences between phasic and tonic REM sleep in stimulus processing by comparing ERPs elicited by frequent standard tones and especially by infrequent deviant tones between phasic and tonic REM sleep. In wakefulness, deviant stimuli are known to elicit two responses of interest, namely, the P3 and MMN. The processing of auditory stimuli between REM sleep and the waking state was also compared with each other.

5.2 Methods

Subjects
Fifteen healthy young volunteers served as subjects (the same subjects as in Study II). Two subjects were excluded from the analysis due to an insufficient number (<20) of ERP responses during either the phasic or tonic periods of REM sleep.

Procedure and stimuli
See Study II.

Recordings
See Study II.

Data analysis
ERPs were calculated for each subject and also separately for the different conditions (reading session, phasic REM sleep, tonic REM sleep) and stimuli (standard, small deviant, large deviant). Baseline-corrected ERP scores were calculated for P1 (50-100 ms), N1 (100-150 ms), MMN (100-200 ms), P210 (150-300 ms), waking P3 (250-600 ms), REM-P3 (350-600 ms) and late negativity (LN) (350-600 ms) waves. The response windows mentioned in the parentheses were divided into 50 ms slices, and the baseline-corrected mean value of each slice served as a score. Scores were obtained for the MMN response from the deviant minus standard difference waves.

Prior to the analyses, all the trials containing an eye movement exceeding +-75 μV within the -675 - 625 ms time window were omitted. All the trials containing motor artefacts within the critical latency range were also excluded.

The classification of the single ERP trials into phasic and tonic REM sleep was based on the occurrence of REMs. A trial was classified as tonic REM sleep when there was no REM 10 s prior to and 5 s after the pitch change. In the case of phasic state, there was at least one REM 0-5 s prior to the pitch change. In all the other cases, a trial was excluded from the analysis.

Statistical analysis
The significance ($p<.05$) of the waves was first tested by a MANOVA in which scores from all the channels were treated as concomitant dependent variables. Next, a channel-by-channel ANOVA was carried out to determine channels at which significance was reached. In the results section, only the ANOVA results were given, but generally only when the MANOVA reached significance. If an ANOVA result was reported in the case of a non-significant MANOVA result, it was separately mentioned.

The differences in ERPs between tonic and phasic REM sleep and wakefulness were tested with a three-way ANOVA with repeated measures for State (wakefulness, phasic REM, tonic REM), Stimulus (standard, small deviant, large deviant), and Channel (Fz, Cz, Pz). The reported significance

values were corrected with the Greenhouse-Geisser correction where appropriate.

5.3 Results

ERPs during phasic REM sleep
Standard tone. None of the responses observed reached significance (Fig. 9).

Small deviant tone. The ERP waves observed failed to reached significance (Fig. 9).

Large deviant tone. The same waves could be observed as in the ERPs to the small deviant tone (Fig. 9). The P210 deflection reached significance at Fz *($F(1,12)=10.68$, $p<.01$)* and Cz *($F(1,12)=15.58$, $p<.01$)*. The REM-P3 approached the significance in the MANOVA analysis *($F(3,10)=3.47$, $p=.059$)*. A channel-by-channel ANOVA showed that it was significant at Pz *($F(1,12)=7.08$, $p<.05$)*.

ERPs during tonic REM sleep
Standard tone. The P1 deflection reached significance at Fz *($F(1,12)=15.84$, $p<.01$)* and Cz *($F(1,12)=5.02$, $p<.05$)* (Fig. 10).

Small deviant tone. The P210 wave reached significance *(Fz: $F(1,12)=5.87$, $p<.05$)* (Fig. 10).

Large deviant tone. The same waves as in the ERPs to the small deviant tone were detected except that the late negativity was almost invisible and a parietally distributed REM-P3 occurred within its latency range (Fig. 10). The P210 was significant for all the channels (Fz: *$F(1,12)=8.26$-28.68, $p<.05$-$.001$*, Cz: *$F(1,12)=14.13$-19.71, $p<.01$*, Pz: *$F(1,12)=7.18$-13.62, $p<.05$)*. In the case of the REM-P3, significance was reached at Cz *($F(1,12)=8.78$-8.83, $p<.05$)* and at Pz *($F(1,12)=6.27$-12.67, $p<.05$-$.01$)*.

ERPs during wakefulness
Standard tone. The ERPs were characterised by a long-lasting negative wave within the latency range of 100-400 ms (Fz: *$F(1,12)=5.31$-7.56, $p<.05$*, Cz: *$F=12.93$-21.31, $p<.01$*, Pz: *$F=8.34$-10.86, $p<.05$-$.01$)*, which was followed by another negative wave (Cz: *$F(1,12)=9.51$, $p<.01$*, Pz: *$F=7.09$-11.65, $p<.05$-$.01$)* (Fig. 11). These waves could not be separated from one another at Pz.

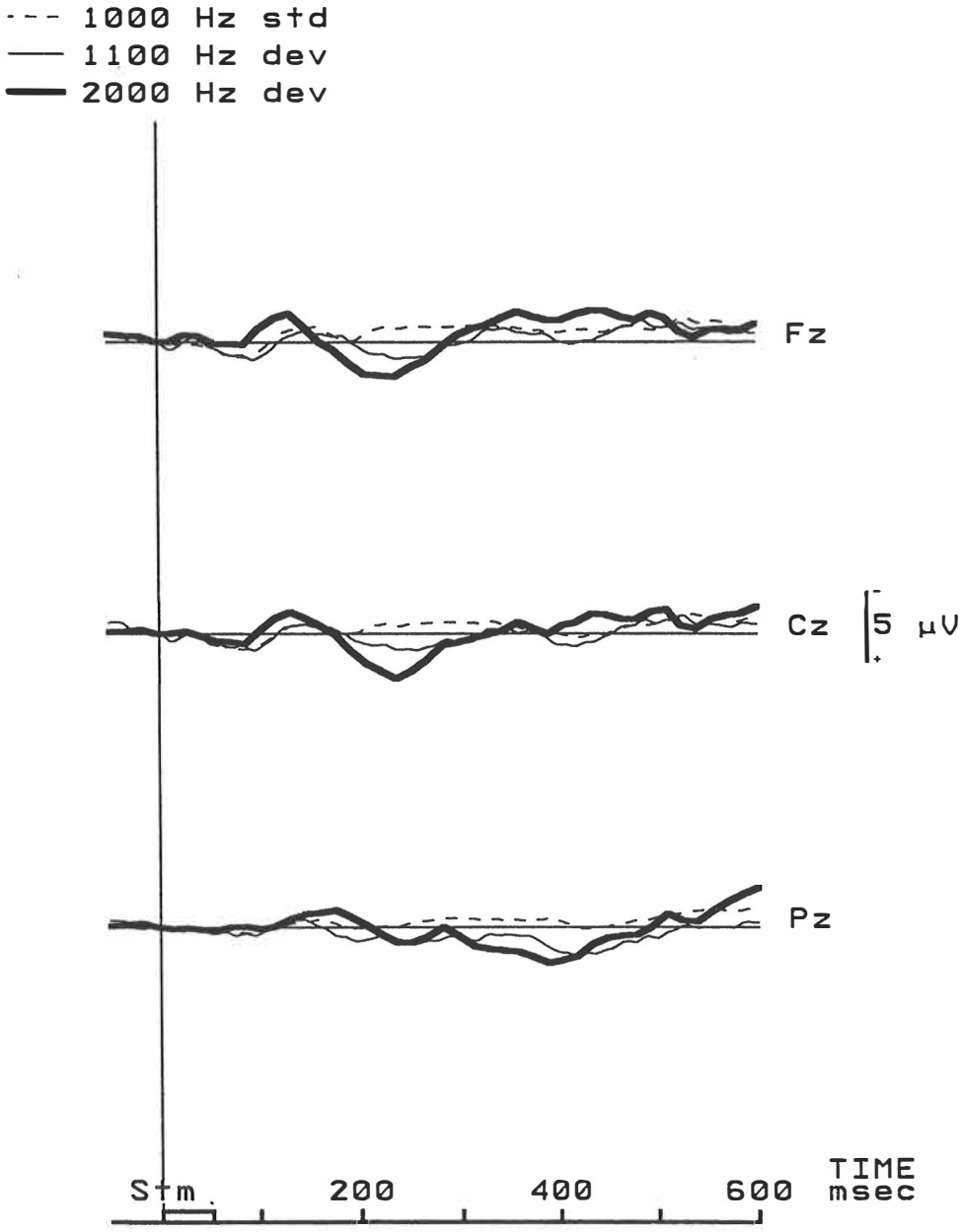

FIGURE 9 Grand-average ERPs (N=13) to the standard tone (thin line, 993 trials), small deviant tone (second thickest line, 458 trials), and large deviant tone (thickest line, 475 trials) during *phasic* REM sleep.

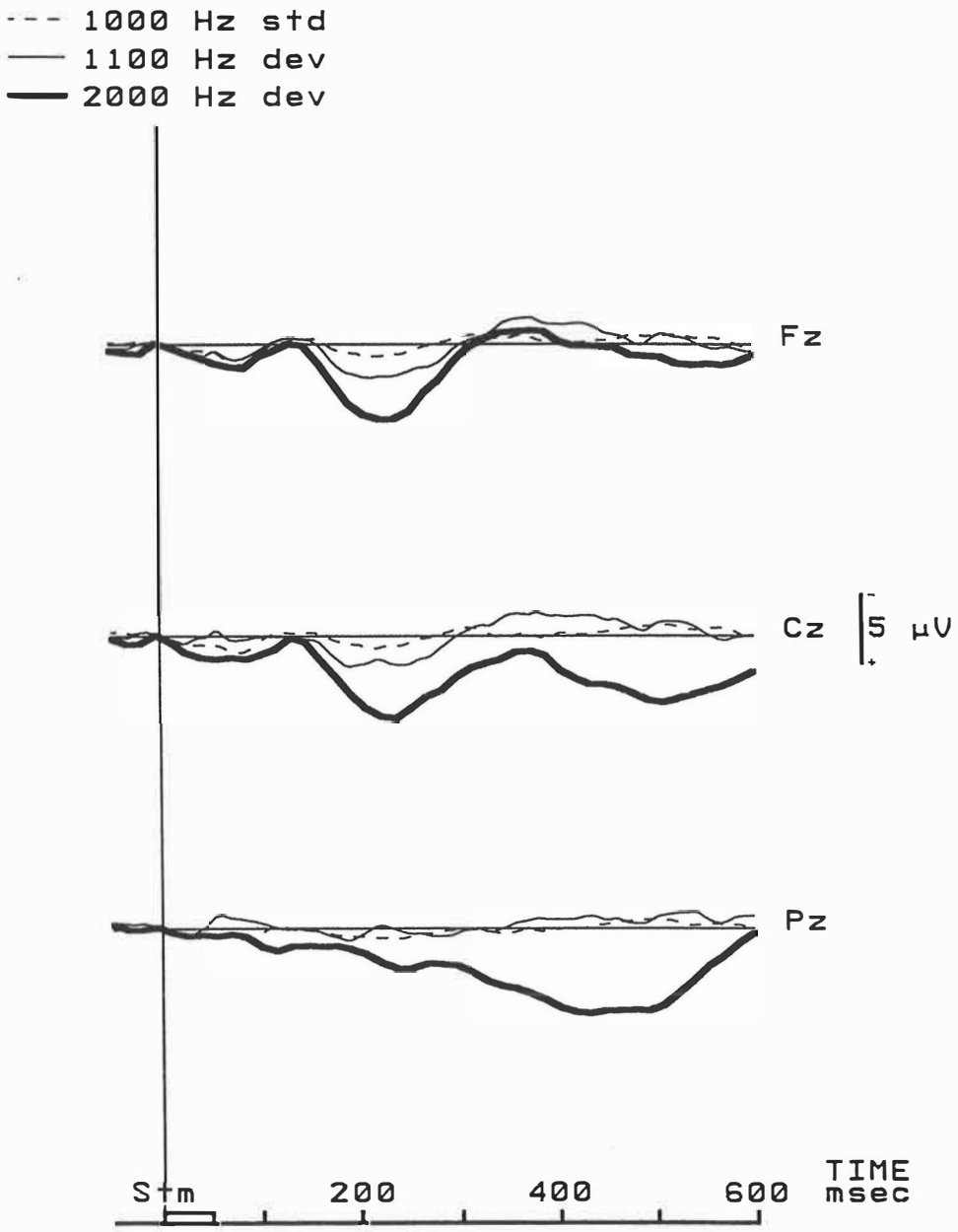

FIGURE 10 Grand-average ERPs (N=13) to the standard tone (thin line, 1037 trials), small deviant tone (second thickest line, 516 trials), and large deviant tone (thickest line, 521 trials) during *tonic* REM sleep.

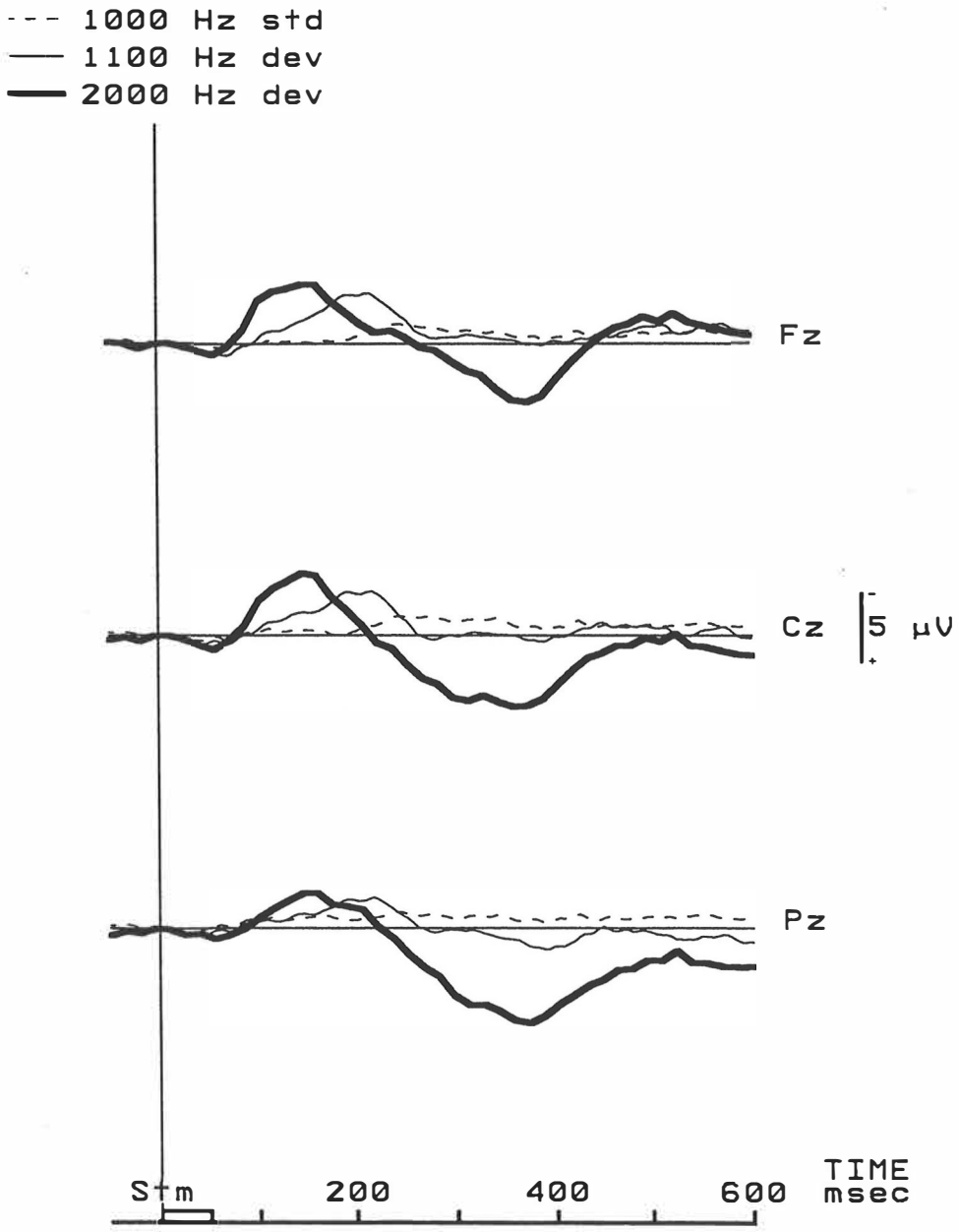

FIGURE 11 Grand-average ERPs (N=13) to the standard tone (thin line, 2631 trials), small deviant tone (second thickest line, 1374 trials), and large deviant tone (thickest line, 1257 trials) during the reading session.

Small deviant tone. The ERPs showed an MMN component (Fz: *F(1,12)=15.75, p<.01*, Cz: *F=11.78, p<.01)* and a small parietally distributed P3 deflection (Pz: *F(1,12)=12.43, p<.01)* (Fig. 11).

Large deviant tone. The ERPs contained an MMN response (Fz: *F(1,12)=20.08-18.53, p<.01*, Cz: *F=20.61-10.82, p<.01*, Pz: *F=5.91-4.73, p<.05)* and a parietally distributed P3 (Fz: *F(1,12)=13.52, p<.01*, Cz: *F=6.65-11.86, p<.05-.01*, Pz: *F=6.37-22.19, p<.05-.01)* (Fig. 11). A reliable late negative wave following the P3 could be detected at Fz *(F(1,12)=6.58-8.88, p<.05).*

ERP differences between phasic REM, tonic REM, and wakefulness

MMN. The ERPs differed between the states within the time windows of the MMN *(F(2,24)=5.20-8.74, p<.01-.05,* ε *=.65543-.79242).* The State × Channel interaction also reached significance within the 150-200 ms time window *(F(4,48)=4.31, p<.05,* ε *=.56203).* Further comparisons showed that the ERPs were more negative during wakefulness than during tonic REM sleep *(F(1,12)=34.41, p<.001).* The other contrasts failed to reach significance. Within the time window of 150-200 ms, the difference wave was more negative during wakefulness than during tonic REM sleep at all the channels (Fz: *F(1,12)=24.46, p<.001*, Cz: *F=39.72, p<.001*, Pz: *F=7.25, p<.05).* The difference curve for wakefulness was also more negative than that for phasic REM sleep at Fz *(F(1,12)=10.49, p<.01)* and Cz *(F(1,12)=11.12, p<.01).* Tonic and phasic REM sleep did not differ significantly.

P210 wave. The amplitude of the P210 wave differed among the states *(F(2,24)=17.75-30.95, p<.001,* ε *=.86007-.93928).* The State × Stimulus × Channel interaction also reached significance within the time window of 150-200 ms *(F(8,96)=3.36, p<.05,* ε *=.39574)* as did the State × Channel interaction within the 200-250 ms time window *(F(4,48)=6.67, p<.01,*ε *=.49504).*

Further comparisons within the 150-200 ms time window revealed that the ERP to the small deviant tone was more positive during tonic REM sleep than during phasic REM sleep at Fz *(F(1,12)=5.03, p<.05)* and during wakefulness at all the channels (Fz: *F(1,12)=23.55, p<.001*, Cz: *F=23.35, p<.001*, Pz: *F=7.31, p<.05).* The ERP of phasic REM sleep was also more positive than that of wakefulness at all the channels (Fz: *F(1,12)=14.11, p<.01*, Cz: *F=10.25, p<.01*, Pz: *F=7.02, p<.05).* The ERPs to the large deviant tone showed no difference between tonic and phasic REM sleep at any channel. The ERPs of REM sleep were, however, more positive than those of wakefulness. In the case of tonic REM sleep, this difference in positivity was found at all the channels (Fz: *F(1,12)=21.88, p<.001*, Cz: *F=19.63, p<.001*, Pz: *F=8.77, p<.05),* and in the case of phasic REM sleep at Fz *(F(1,12)=36.30, p<.001)* and Cz *(F(1,12)=14.36, p<.01).*

Further tests within the latency of 200-250 ms showed that the ERPs were more positive during tonic REM sleep than during phasic REM sleep at Fz *(F(1,12)=16.42, p<.01)* and Cz *(F(1,12)=8.75, p<.05)* and during wakefulness at all the channels (Fz: *F(1,12)=63.32, p<.001*, Cz: *F=52.64, p<.001*, Pz: *F=11.10, p<.01).* The ERPs of phasic REM sleep were also more positive than those of

wakefulness at all the channels (Fz: $F(1,12)=36.46$, $p<.001$, Cz: $F=30.35$, $p<.01$, Pz: $F=8.94$, $p<.05$).

P3 wave. The parietally distributed P3 wave differed among the states within the latency range of 350-400 ms ($F(2,24)=5.48$, $p<.05$, $\varepsilon = .71677$). The ERPs were more positive during wakefulness than during tonic ($F(1,12)=5.64$, $p<.05$) and phasic REM sleep ($F(1,12)=10.92$, $p<.01$). This state effect tended to be the most pronounced for the large deviant tone. No reliable difference was found between the tonic and phasic periods of REM sleep.

The State × Stimulus interaction reached significance within the time window of 400-450 ms ($F(4,48)=2.90$, $p<.05$, $\varepsilon = .74993$). The ERPs to the large deviant tone were more positive during tonic than phasic REM sleep ($F(1,12)=5.52$, $p<.05$). The other contrasts failed to reach significance.

The State × Stimulus × Channel interaction reached significance within the latency range of 450-550 ms ($F(8,96)=3.23$-3.36, $p<.05$, $\varepsilon = .40496$-$.43942$). The ERP to the large deviant tone was more positive during tonic than phasic REM sleep at Cz ($F(1,12)=8.93$-17.19, $p<.05$-$.01$) and Pz ($F(1,12)=7.02$-10.87, $p<.05$-$.01$) and during wakefulness at Cz ($F(1,12)=6.52$-7.32, $p<.05$). The contrasts between phasic REM sleep and wakefulness failed to reach significance.

The maximum amplitudes of the parietally distributed waking P3 and tonic REM-P3 did not differ significantly from each other. The peak latency of the waking P3 (369 ms, SD=64.0) was, however, significantly shorter than that of the tonic REM-P3 (439 ms, SD=54.5) ($F(1,12)=5.59$, $p<.05$).

5.4 Discussion

The present study showed that the phasic and tonic periods of REM sleep differ in terms of the neurophysiological processing of auditory stimuli. This difference was seen for the P210 at Fz and Cz and for the REM-P3 to the large deviant tone, especially at Cz and Pz. Both waves were larger during tonic than during phasic REM sleep. The REM-P3 during the tonic state resembled the parietally distributed waking P3, with the exception that the peak latency of the REM-P3 was longer. Prior to the P3 latency, these ERPs were dissimilar, however. A reliable MMN occurred only in wakefulness and a P210 occurred only in sleep.

Our results are consistent with findings indicating that the brain is more preoccupied with ongoing mental activity during phasic than during tonic REM sleep (Berger & Oswald, 1962; Dement & Wolpert, 1958; Firth & Oswald, 1975; Karacan et al., 1966; Pivik & Foulkes, 1966; Taylor et al., 1985; Weinstein et al., 1988). They also support the hypothesis of Bastuji et al. (1995) that the alternation between phasic and tonic REM sleep explained the inconsistency in the occurrence of the PS-P3 in their study. A central issue is the function of the REM-P3 in this context. One hypothesis is that it is a counterpart of the waking P3b. The findings supporting this interpretation are the similarity in the

topography and sensitiveness to the stimulus probability, the magnitude of the stimulus deviation, and the availability of attentional resources. There is no empirical evidence contraindicating this hypothesis. The longer peak latency of REM-P3 compared with that of the waking P3b is a sensible finding, for cognitive functions are known to become slower as alertness decreases (Dinges & Kribbs, 1991). The hypothesis that the waking and REM-P3 reflect different neural processes is based more on the suggestion that stimulus evaluation is too elaborate form of stimulus processing to occur during sleep. Previous studies with behavioural (Burton et al., 1988; Williams et al., 1966) and subjective (Burton et al., 1988; Hoelscher et al., 1981) measures have, however, shown that complex stimulus processing is possible at least during some moments of sleep. In light of this finding, the occurrence of the P3b wave during REM sleep can not be considered a surprising result.

One question of importance is whether the difference between phasic and tonic REM sleep in the REM-P3 could be due to something other than a difference in attentional resources. The finding that the P210 wave was smaller during phasic than during tonic REM sleep suggests that the deviant stimuli were processed differentially by the brain already during a phase which is apparently not dependent on attentional resources. In addition, some evidence suggests that the processing of an auditory input is attenuated to some extent prior its arrival in the brain during REMs in REM sleep because of twitches in the ear muscles (Baust, Gerlucchi, & Moruzzi, 1964; Pessah & Roffwarg, 1972). Thus it seems that the difference in the REM-P3 wave found between phasic and tonic REM sleep can not be exclusively attributed to the difference in the availability of the attentional resources. It is, however, probable that differences between the phasic and tonic states in stimulus processing and mental state are closely connected. The temporarily attenuated sensitivity to external stimuli can be considered to contribute to an immersion in dream content during phasic REM sleep.

Another explanation for the ERP differences observed between phasic and tonic REM sleep could be that tonic REM sleep during which no REMs occurred could not be reliably distinguished from sleep NREM sleep stages 1 and 2. The scoring of REM sleep was based on the criteria of Rechtschaffen and Kales (1968), and they are arbitrary and do not absolutely ensure discrimination between REM sleep and sleep stages 1 and 2. Nevertheless, they are widely used and exact. The rules can be considered to ensure that tonic REM sleep can be differentiated from NREM sleep in most cases. The facts that the EMG was at its lowest level and that prominent slow eye movements, vertex waves, and movement arousals typical of stage 1 sleep were absent during the REM epochs assured that tonic REM sleep was reliably discriminated from stage 1 sleep. Secondly, the P210 would not have been larger during tonic REM sleep than during phasic REM sleep if tonic REM sleep had not been reliably distinguishable from stage 1 sleep (see Bastuji et al., 1995). The ERP data also suggest that tonic REM sleep was successfully differentiated from stage 2 sleep. ERPs to distinctive stimuli are known to contain N350, N550, P900 waves during stage 2 sleep, but the present ERPs of REM sleep showed no signs of these waves. In addition, the REM epochs of 20

s showed no EEG events typical of stage 2 sleep (K-complexes, sleep spindles); this finding also supports the view that these epochs did not represent stage 2 sleep.

The MMN response seemed to occur only in the reading session. This finding is inconsistent with the previous studies on the MMN response during REM sleep (Campbell et al., 1992; Loewy et al., 1996). In the present study, a tendency for a negative wave was observed within the MMN latency range during both phasic and tonic REM sleep, but the same was true also for the standard tone. It is possible that the tendency for an MMN response was attenuated by the following P210 wave that possibly overlapped the negative deflection to the deviant tones during REM sleep. This positivity was much greater for the deviant tones than for the standard ones. In phasic REM sleep, it was totally absent for the standard tone. The standard tones of Campbell et al. (1992) and Loewy et al. (1996) elicited very similar P210 waves when compared with deviant tones. This difference in the elicitation of the P210 to the standard tone between the present and these previous studies may be due to the smaller probability of the standard tone in the previous studies than in the present one.

Concluding remarks

The present results support the hypothesis that external stimuli have a more open access to awareness during tonic REM sleep than during phasic REM sleep. It is likely that this difference is closely connected to the difference in the orientation to dreams.

6 STUDY IV

Mismatch negativity during objective and subjective sleepiness

6.1 Introduction

Thus far, there are more studies on the MMN response during sleep than during sleepiness. Two well-reported studies with young human adults presented findings on the MMN response during sleepiness (Paavilainen et al., 1987; Winter et al., 1995) but neither of these studies provided optimal stimulus conditions for the occurrence of the MMN response. Secondly, these studies included only electrophysiological measures in spite of the fact that a person's feeling of alertness, as well as voluntary behavioural responding, is altered during the wake/sleep transition. These different measures of sleepiness do not always match with each other (e.g., Dement et al., 1978; Johnson et al., 1991; Sugerman et al., 1985). Interestingly, Lang et al. (1995) reported data from two subjects whose subjective sleepiness and performance (reading speed) were measured during the night-time recording of MMN. The results suggested that changes in the MMN amplitude are associated with changes in performance and subjective sleepiness before electrophysiologically defined sleep.

In the present experiment, the focus was especially on the question of whether the attenuation of the MMN recorded under optimal stimulus conditions commences already in sleepiness when conscious awareness of external events is less impaired than during actual sleep. The occurrence of MMN, and also the following P3, was examined for unattended auditory stimuli during both objective and subjective sleepiness. A short ISI (450 ms) and a highly frequent standard tone (p=.90) was used to ensure that the memory trace of the standard tone was strong when the input of a deviant tone arrived in the auditory cortex. In addition a small stimulus change (5 %) being applied, a large stimulus change (20 %) was used to ensure that the stimulus

difference would be easily detected by the brain. The procedure also made it possible to collect a sufficient number of trials for the separation of the small amplitude MMN from spontaneous electroencephalography (EEG) events reliably during sleepiness. Finally, performance in a reaction time task including attended auditory and visual target stimuli was measured simultaneously with the MMN recording to the unattended stimuli so that any impairment in voluntary responding could be assessed in connection with the possible attenuation of the MMN during sleepiness.

6.2 Methods

Subjects
Twelve healthy, right-handed volunteers, aged 21-31 years, spent one night in the laboratory trying to stay awake. Drugs and alcohol were not permitted for 24 h prior to the experiment. The data on one subject had to be removed from the analyses because of a failure of the continuous EEG, electro-oculographic (EOG), and electromyographic (EMG) recording (see the Section on recordings).

Protocol
The subjects slept normally during the night preceding the experiment. They sat in a comfortable chair in a dim room during the recording sessions. The night (1900-0600 or 0800) consisted of 6-7 recording sessions of 1 h during which the subjects performed a reaction time task (see below). The subjects practised the task for 30 min before the beginning of the experiment. The training period ended 30 min prior to the experiment. During the experiment, the subjects were presented the word "arvio" (assessment) every third minute, after which they gave one number (1-7) from the Stanford Sleepiness Scale (SSS) (Hoddes, Zarcone, Smythe, & Dement, 1973). This number represented their subjective sleepiness at that moment. The subject was immediately awakened when a sleep spindle or K-complex appeared. There was always a 1 h pause between two consecutive recording sessions.

Stimulus input outside the attentional focus
The stimuli of an oddball paradigm consisted of a repetitive standard tone of 1000 Hz (p=90%), a small deviant tone of 1050 Hz (p=5%), and a large deviant tone of 1200 Hz (p=5%). These probabilities were determined so that they did not include those periods during which target stimuli were presented (see below). The order of the tones was randomised, except that there were always at least two standard tones between two consecutive pitch changes. All the stimuli had an intensity of 55 dB, a duration of 50 ms, and a rise/fall time of 10 ms. The constant ISI was 450 ms. The stimuli were always presented to the left ear, and the subjects were told that they did not need to attend or respond to these stimuli.

Stimulus input in the attentional focus

The subject's task was to ignore the auditory stimuli presented to the left ear and to press a button upon detection of either an auditory target presented to the right ear or the flash of a light located 1.3 m at eye level in front of them. The auditory target was a 60 dB 500 Hz tone having a duration of 100 ms and a rise-and-fall-time of 5 ms. The target tone was repeated six times if the subject had not responded before. The ISI between the repetitions was 900 ms. The response always ceased the train of the target tones. The visual target consisted of a 20 cm circle of 20 green leds having an intensity of 60 W. Normally, each led went on one at a time, and the direction of rotation was clockwise. One led was on for 50 ms and the next led went on immediately after the first was turned off. In the case of the target, only every second led went on. These double jumps continued for 4.6 s if the subject did not respond. They ceased immediately after the response. The auditory and visual target trains were presented randomly with the exception that the maximum number for consecutive presentations of one type of target train was nine. Thus the subjects were unable to anticipate whether an auditory or visual target train would start next. In addition, the interval between two consecutive target trains varied randomly between 2 and 43 s. Therefore there was 2-3 target trains per minute. The target trains occurred less frequently than the pitch changes in the unattended stimulus input. Both target trains were synchronised to the stream of the unattended auditory input so that they commenced between two consecutive standard stimuli presented in the unattended input. There were always at least four consecutive standard stimuli (2025 ms) between any target stimulus and the next pitch change in the unattended auditory input. The interval from any pitch change in the unattended auditory input to the next target stimulus contained a minimum of two consecutive standard stimuli (1125 ms). Otherwise both of these intervals varied randomly. Thus, ERPs to the targets in the attended input and the pitch changes in the unattended auditory input did not overlap.

Recording

The ERP recordings were made with AgAg/Cl electrodes and attached to Fz, Cz, Pz, and the right mastoid (M2). The nose was used for reference. The time constant and low-pass filter were 1 s and 100 Hz, respectively. The impedance was maintained below 5 kΩ. The EEG was stored for 500 ms before and 700 ms after the pitch changes. The sampling rate was 200 Hz for the ERP data. Separate data were collected for sleep stage scoring according to the criteria of Rechtschaffen and Kales (1968). The data contained continuously recorded EEG, EOG, and EMG signals (sampling rate 250 Hz). The sleep state scoring was based on 30 s data epochs.

Classification of trials

All the trials containing a deflection exceeding +-100 μV at any channel within the window of 500 ms prior to and 500 ms after the deviant tones were automatically omitted. The accepted single EEG epochs were selectively averaged after changes in the subjective and objective measures of sleepiness.

In the case of subjective sleepiness, a score for each 3 min epoch (ratings were given every 3 min) was determined by averaging ratings given at the beginning and end of this period. Scores 1-2 were defined to represent the alert state, scores 2.5-5 defined the intermediate state ("not alert/not sleepy"), and scores 5.5-7 represented the sleepy state. Table 1.1 shows the number of trials in each category and the distribution of the trials among the objectively defined categories of sleepiness. The results were based on the data from 10 subjects because one subject reported no alert state during the experiment. When the recording had to be interrupted for some reason during a 3 min epoch, the trials of this period were not included in the ERPs. All the ERP trials that occurred during the 30 s epochs scored as stage 2 sleep were removed prior to the averaging of the ERPs.

In the case of objective sleepiness, the 30 s epochs of the continuously recorded EEG, EOG, and EMG data were divided into the three categories: wakefulness, drowsiness, and stage 1 sleep. An epoch was classified into the drowsiness category when it contained at least one slow eye movement (SEM) but could not be classified as stage 1 sleep according to the criteria of Rechtschaffen & Kales (1968). SEMs have been shown to be closely associated with drowsiness (e.g., Ogilvie, McDonagh, Stone, & Wilkinson, 1988). Sleep stage 1 was defined according to the traditional criteria (Rechtschaffen & Kales, 1968). Table 1.2 shows the number of trials in each category and the distribution of the trials among the subjectively defined categories of sleepiness. The number of trials was too small for obtaining reliable ERPs in stage 1 sleep.

TABLE 1.1 Number of trials in each category of *subjectively* defined sleepiness and the distribution of the trials according to *objectively* defined sleepiness.

	Alert	Interm.	Sleepy
Wakefulness	7846	8144	2787
Drowsiness	24	589	2604
Stage 1 sleep	0	9	213
Uncertain	0	178	467
Total	7870	8920	6071

TABLE 1.2 Number of trials in each category of *objectively* defined sleepiness and the distribution of the trials according to *subjectively* defined sleepiness.

	Wakefulness	Drowsiness	Stage 1 sleep
Alert	7416	11	0
Interm.	9619	487	8
Sleepy	3599	3635	183
Uncertain	1178	1334	208
Total	21812	5467	399

Response scoring and statistical analyses
The baseline-corrected ERP scores were calculated for the MMN response (100-200 ms) and, if necessary, for the immediately following P3 (200-400 ms). The response windows of these waves were divided into 50 ms time slices, and the mean value of each slice was used as a score. The MMN scores were calculated as the difference between the deviant and standard waves.

The effect of sleepiness on the responses was tested with a two- or three-way ANOVA involving the level of sleepiness, electrode location, and the magnitude of stimulus deviation as within-subject variables. The Greenhouse-Geisser correction was used where appropriate.

A non-parametric Friedman two-way ANOVA was applied to the reaction-time data because the small number of stimulus presentations did not allow for a normal distribution of scores.

6.3 Results

Subjective sleepiness
MMN. The MMN amplitude significantly decreased as subjective alertness decreased *(F(2,18)=4.57-4.62, p<.05,* ε *=0.7941-0.7205)* (Figs. 12.1 & 12.2 & Table 2). In addition, the Subjective sleepiness × Channel interaction was significant *(F(6,22)=7.77-5.63, p<.01,* ε *=0.4325-0.4150).* Table 2 shows that the effect of sleepiness on the MMN amplitude was stronger at Fz and Cz than at M2. Additional tests showed that the MMN was significantly affected by sleepiness at Fz *(F(2,18)=9.44-5.13, p<.05,* ε *=0.57425-0.33383)* and Cz *(F(2,18)=5.68-5.13, p<.05,* ε *=0.74825-0.75659)* within the 100-200 ms latency range. Subjective sleepiness did not have a significant effect on the MMN at either Pz or M2. The contrasts showed that the MMN amplitude was significantly lower during the sleepy state than during the alert state (Fz: *F(1,9)=9.39-5.55, p<.05,* Cz: *F=6.28, p<.05)* and the intermediate state (Fz: *F(1,9)=10.98-9.00, p<.01-.05,* Cz: *F=15.68-15.19, p<.01).* The MMN amplitude did not differ between the alert and intermediate states.

P3. The main effect of the level of sleepiness on the P3 to the large deviant tone was not significant (Fig. 13). The Subjective sleepiness × Channel interaction was, however, significant *(250-300 ms window: F(4,36)=4.23, p<.05,* ε *=0.5996).* Fig. 13 shows that the effect of sleepiness on the P3 was the most pronounced at Pz, where it was almost invisible in the sleepy state. A decrease in the P3 occurred reliably only at Pz during the alert/sleepy transition *(F(2,18)=3.77, p<.05,* ε *=.9344).*

Behavioural responsiveness. Table 3 shows the changes in behavioural responsiveness as self-reported sleepiness increased. The RTs to the auditory *(chi-square(2)=20.00, p<.001)* and visual targets *(chi-square(2)=20.00, p<.001)* became slower as sleepiness increased. Further analyses showed that the RTs

differed between the alert state and the intermediate state *(the auditory target: chi square(1)=10.00, p<.01, the visual target: chi square(1)=10.00, p<.01)* as well as between the intermediate state and the sleepy state *(the auditory target: chi square(1)=10.00, p<.01, the visual target: chi square(1)=10.00, p<.01)*. The increase in the RTs averaged 12.2% during the alert/intermediate transition and 50.9% during the alert/sleepy transition. The probability of lapses (no response) to the visual target increased as alertness decreased *(chi-square(2)=20.00, p<.001)*. The subjects were able to respond to almost all the auditory targets, even during the sleepy state.

TABLE 2 Mean (SD) amplitudes of the MMN to small (5%) and large (20%) pitch deviance within two time windows during *subjectively* rated states of alertness/sleepiness.

Stimulus/ Channel	100-150 ms			150-200 ms		
	Alert	Interm.	Sleepy	Alert	Interm.	Sleepy
1050 Hz						
Fz	-0.40	-1.08	0.58	-0.95	-1.66	-0.25
	(1.88)	(1.00)	(1.44)	(1.21)	(1.45)	(1.24)
Cz	-0.27	-0.76	0.31	-0.71	-1.12	-0.25
	(2.34)	(1.15)	(1.18)	(1.57)	(1.48)	(0.94)
Pz	-0.60	-0.26	0.33	0.09	-0.32	0.14
	(2.22)	(1.11)	(0.99)	(1.59)	(1.26)	(0.63)
M2	1.00	0.67	0.70	1.34	0.97	0.92
	(1.03)	(1.21)	(0.67)	(1.25)	(1.17)	(0.86)
1200 Hz						
Fz	-3.29	-2.26	-0.99	-3.20	-2.51	-0.54
	(1.74)	(1.31)	(2.06)	(2.13)	(1.52)	(2.64)
Cz	-3.14	-2.18	-1.32	-2.95	-2.07	-0.37
	(1.64)	(1.61)	(1.08)	(1.59)	(1.13)	(2.34)
Pz	1.63	-0.73	-0.35	-1.38	-0.86	0.48
	(1.50)	(1.46)	(1.21)	(0.77)	(0.81)	(1.77)
M2	1.35	1.77	1.17	1.39	1.63	1.00
	(0.79)	(0.51)	(0.75)	(1.58)	(1.12)	(0.91)

TABLE 3 Voluntary behavioural responsiveness mean (SD), as a function of *subjectively* rated alertness/sleepiness. N=10 in all cases. Interm. = the intermediate state. RT=reaction time.

Performance in RT task	Alert	Interm.	Sleepy
RTs to auditory target (ms)	411.2 (59.4)	454.8 (48.3)	626.5 (103.2)
RTs to visual target (ms)	620.3 (86.7)	705.5 (103.4)	926.63 (111.4)
Lapses to auditory target (%)	0.0 (0.0)	0.0 (0.0)	0.74 (1.9)
Lapses to visual target (%)	1.8 (2.3)	10.8 (13.2)	40.1 (13.7)

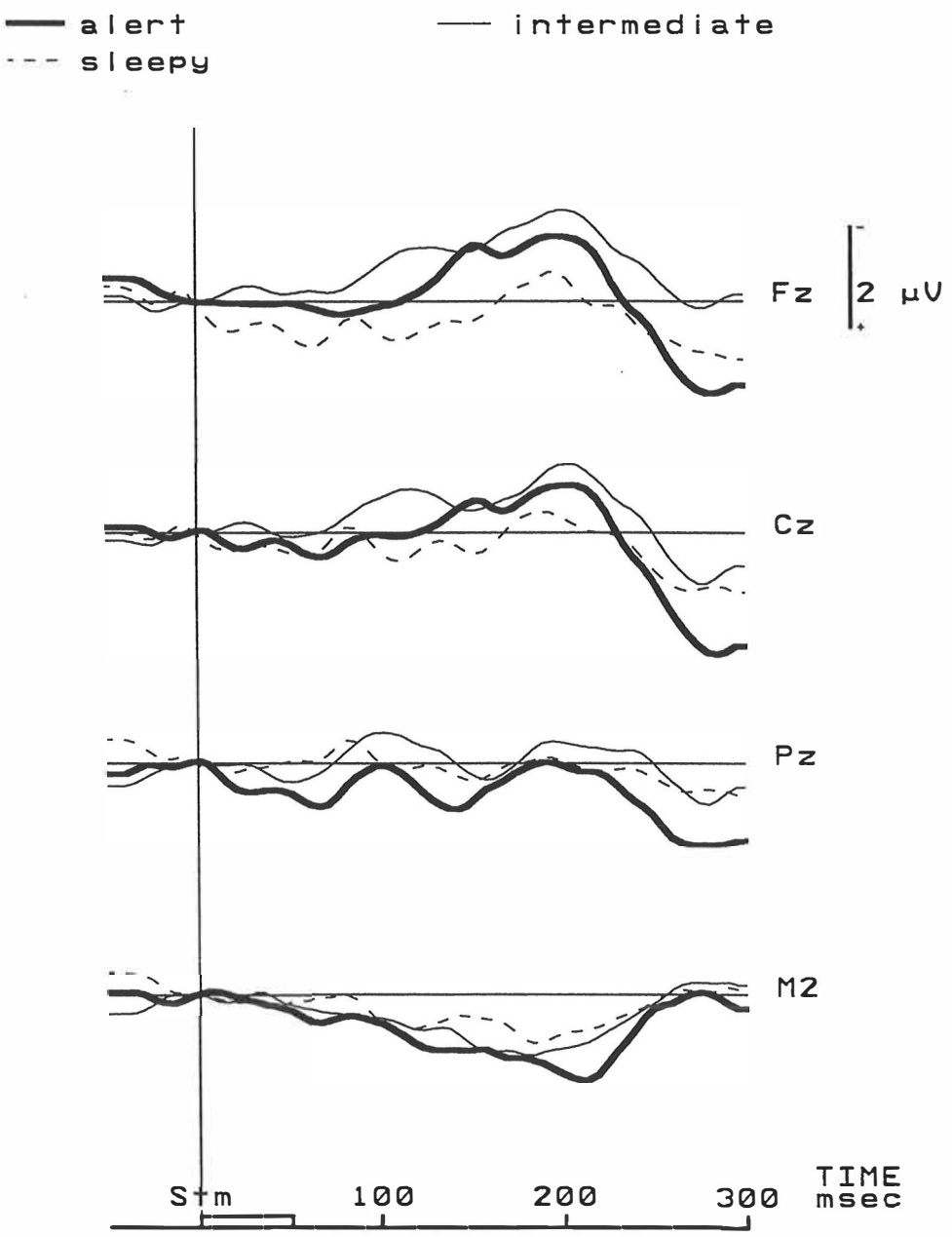

FIGURE 12.1 Grand-average difference waveforms (N=10) derived by subtracting the ERPs to the standard tone from the ERPs to the *small* pitch deviation during the *subjectively* rated alert (thick solid line, 3800 trials), intermediate (thin solid line, 4441 trials), and sleepy (dotted line, 3091 trials) state.

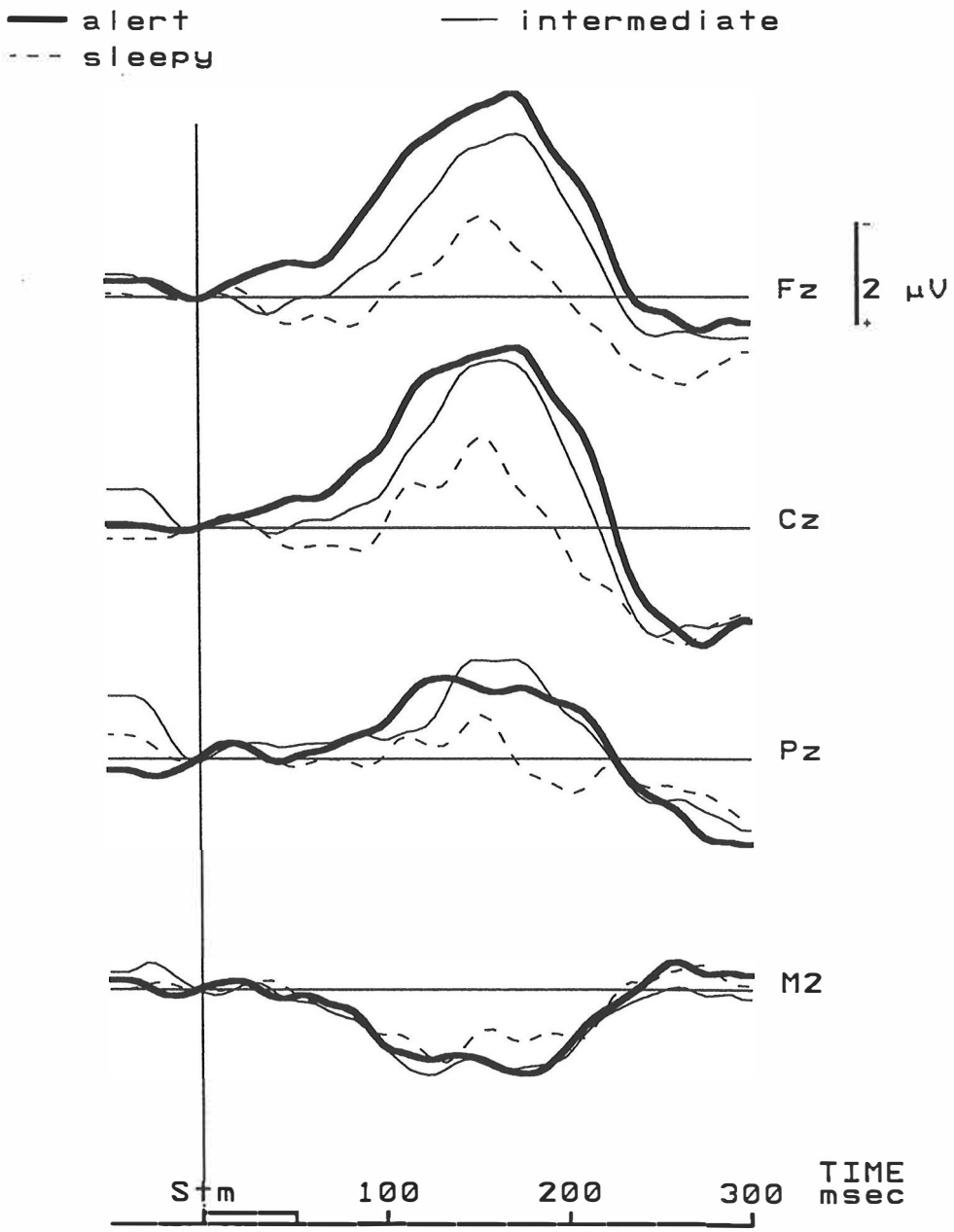

FIGURE 12.2 Grand-average difference waveforms (N=10) derived by subtracting the ERPs to the standard tone from the ERPs to the *large* pitch deviation during the *subjectively* rated alert (thick solid line, 4070 trials), intermediate (thin solid line, 4479 trials), and sleepy (dotted line, 2926 trials) state.

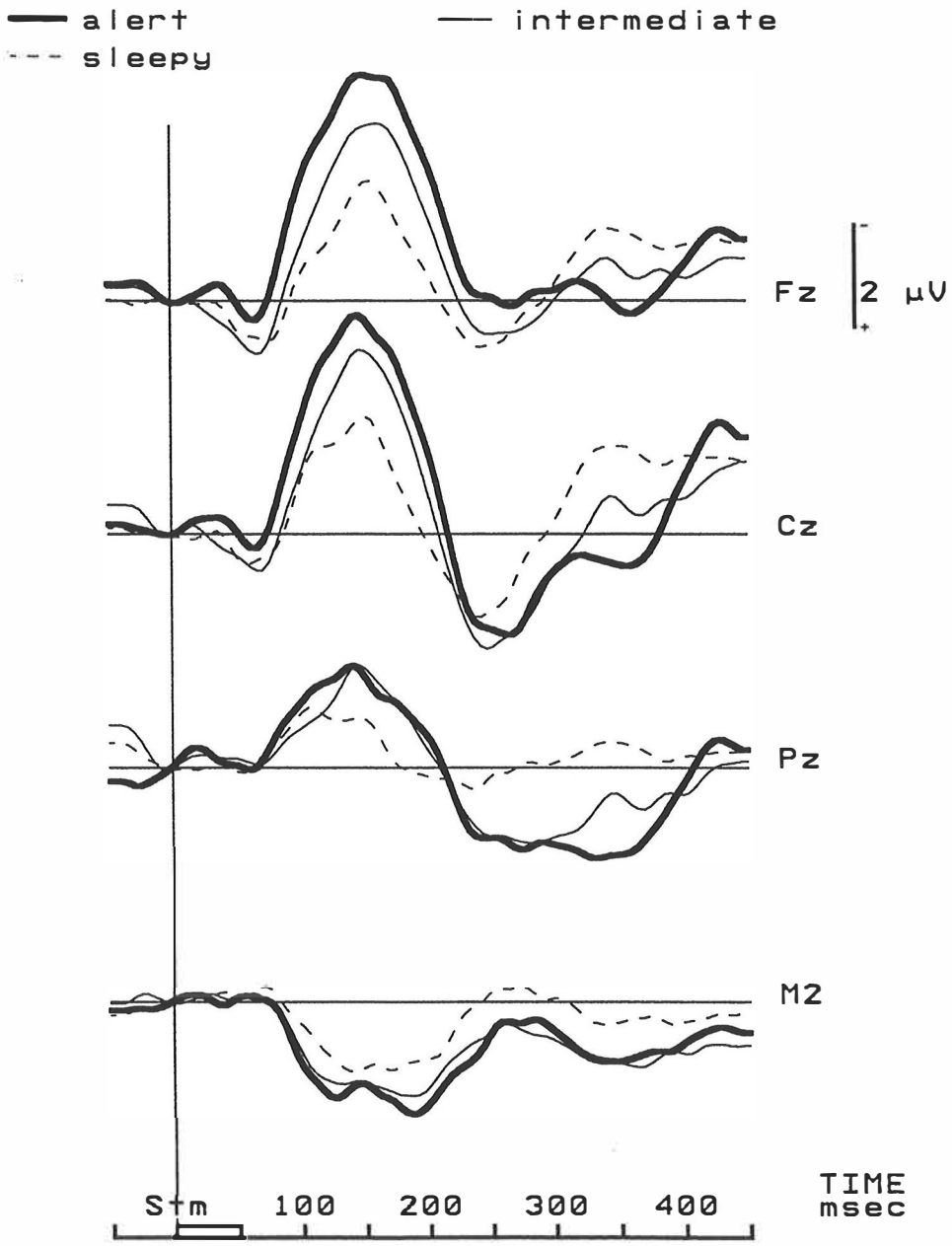

FIGURE 13 Grand-average ERPs (N=10) to the *large* pitch deviation during the *subjectively* rated alert (thick solid line, 4070 trials), intermediate (thin solid line, 4479 trials), and sleepy (dotted line, 2926 trials) state.

Objective sleepiness

MMN. The MMN amplitude decreased with the decrease in alertness *(F(1,10)=5.69-10.00, p<.05)* (Figs. 14.1 & 14.2 and Table 4). The Objective sleepiness × Channel interaction was significant *(F(3,30)=10.59-14.43, p<.001, ε =0.7092-0.6446).* The effect of sleepiness on the MMN response was greater at Fz and Cz than at M2. Additional tests showed that the level of objective sleepiness was significant at Fz *(F(1,10)=15.15-14.13, p<.01)*, Cz *(F(1,10)=8.42-14.56, p<.05-.01)*, and Pz *(F(1,10)=5.00-8.69, p<.05)* within the 100-200 ms latency range and at M2 *(F(1,10)=6.33, p<.05)* within the 150-200 ms time window. The other interactions were not significant.

TABLE 4 Mean (SD) amplitudes of the MMN to small (5%) and large (20%) pitch deviance within two time windows during *physiologically* defined alertness/sleepiness.

Stimulus/ Channel	100-150 ms		150-200 ms	
	Wakefulness	Drowsiness	Wakefulness	Drowsiness
1050 Hz				
Fz	-0.61	0.53	-1.46	-0.29
	(0.72)	(1.45)	(0.89)	(1.46)
Cz	-0.44	0.86	-1.09	0.20
	(0.79)	(1.25)	(0.85)	(1.27)
Pz	0.02	1.07	-0.24	0.60
	(0.78)	(1.84)	(0.54)	(1.46)
M2	0.91	0.51	1.15	0.13
	(0.65)	(1.66)	(0.78)	(2.04)
1200 Hz				
Fz	-2.33	-1.30	-2.64	-0.70
	(1.27)	(1.21)	(1.42)	(2.06)
Cz	-2.20	-0.68	-3.44	-0.16
	(1.20)	(2.11)	(1.38)	(2.83)
Pz	-0.84	0.38	-1.81	0.68
	(0.67)	(1.62)	(1.22)	(2.44)
M2	1.57	1.35	1.41	1.08
	(0.37)	(0.74)	(1.05)	(1.27)

P3. The main effect of the level of sleepiness on the P3 to the large deviant tone was non-significant but the Objective sleepiness × Channel interaction *(200-300 ms window: F(2,20)=6.60-5.28, p<.05, =0.64337-0.8197)* reached significance. As shown in Fig. 15, the effect of decreased objective alertness was the most prominent at Pz, where the P3 became invisible during the drowsy state. Further channel-specific tests did not show a reliable attenuation of the P3 wave at any channel, however.

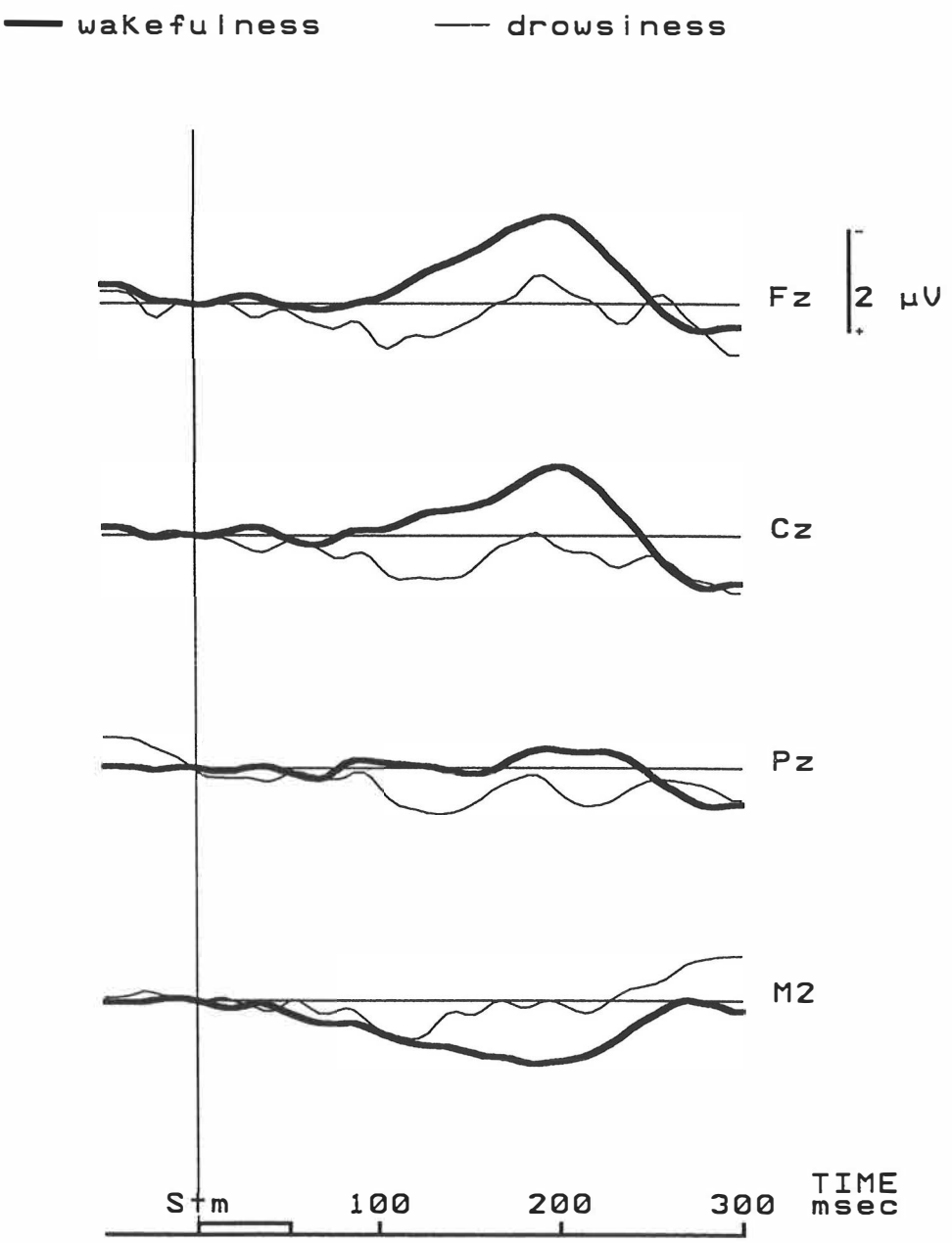

FIGURE 14.1 Grand-average difference waveforms (N=11) derived by subtracting the ERPs to the standard tone from the ERPs to the *small* pitch deviation during the *objectively* defined wakefulness (thick line, 10806 trials) and drowsiness (thin line, 2772 trials).

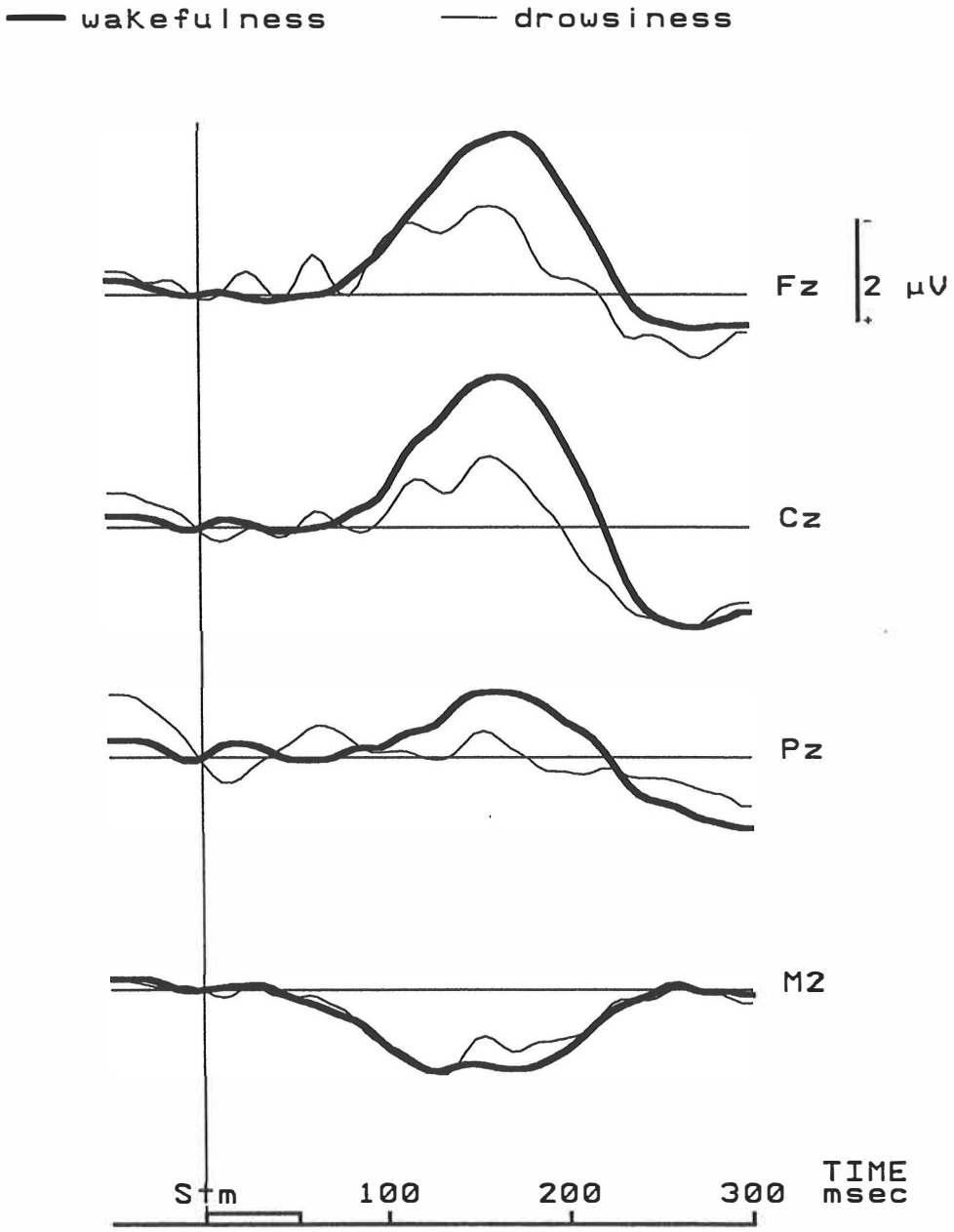

FIGURE 14.2 Grand-average difference waveforms (N=11) derived by subtracting the ERPs to the standard tone from the ERPs to the *large* pitch deviation during the *objectively* defined wakefulness (thick line, 11006 trials) and drowsiness (thin line, 2695 trials).

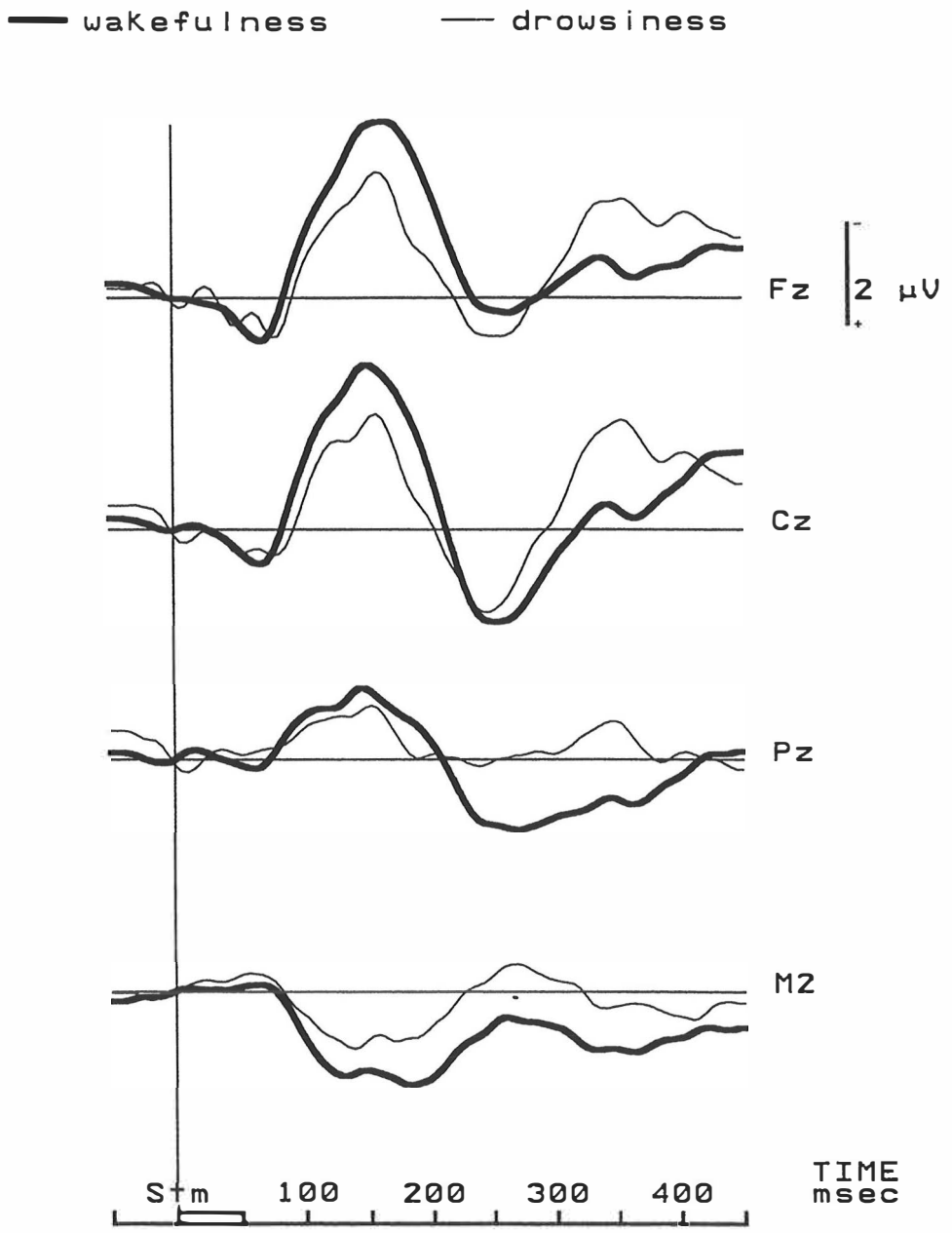

FIGURE 15 Grand- average ERPs (N=11) to the *large* pitch deviation during the *objectively* defined wakefulness (thick line, 11006 trials) and drowsiness (thin line, 2695 trials).

Behavioural responsiveness. Table 5 shows the change in behavioural responsiveness as the physiologically defined alertness became lower. The RTs to the auditory *(chi-square(1)=11.00, p<.001)* and visual targets *(chi-square(1)=7.36, p<.01)* were slower during drowsiness than during wakefulness. The impairment in the RT averaged 43.3%. The probability of lapses to the visual target increased during the wake/drowsiness transition *(chi-square(1)=11.00, p<.001)*. Sleepiness had no significant effect on lapses to the auditory target. During both states, the subjects were able to respond to almost all the auditory targets.

TABLE 5 Voluntary behavioural responsiveness mean (SD), as a function of *physiologically* defined alertness/sleepiness. Drow. = drowsiness, S1 = stage 1 sleep. RT=reaction time.

Performance in RT task	Wake (N=11)	Drow.(N=11)	S1 (N=7-8)
RTs to auditory target (ms)	445.2 (62.5)	693.6 (128.6)	1230.6 (310.9), N=7
RTs to visual target (ms)	690.3 (100.6)	903.0 (301.4)	-
Lapses to auditory target (%)	0.2 (0.3)	1.3 (2.4)	3.9 (6.7), N=7
Lapses to visual target (%)	6.2 (3.5)	58.18 (17.0)	100.0 (0.0), N=8

6.4 Discussion

The most important and new findings of the present study were that the MMN was markedly attenuated: i) in sleepiness even when optimal stimulus conditions for the MMN elicitation are used, ii) in sleepiness regardless of whether sleepiness is defined objectively or subjectively, iii) in sleepiness more clearly at Fz and Cz than at M2, and iv) in sleepiness characterised by severely impaired voluntary behavioural responding. In addition, the present study showed that the P3 for pitch changes among an auditory input, which is not actively attended, declines during sleepiness, especially at Pz.

MMN during sleepiness

In light of the present observations that the MMN response is reduced in sleepiness even under optimal stimulus conditions, it is not surprising that MMN has been difficult to demonstrate during sleep in previous studies. It is possible that some part of the decline in the negative wave within the MMN latency can be attributed to a reduction in the N2b wave that overlaps the MMN response, especially when the eliciting stimulus change is salient (Näätänen, Simpson, & Loveless, 1982). Thus this overlapping may especially occur for the ERPs to the large deviant tone. On the other hand, the disappearance of the N2 wave to the small deviant tone at Fz during objective

sleepiness suggests that not only the N2b, but also the MMN, was affected by sleepiness.

The present data tentatively suggest that the frontal subcomponent of the MMN response may more vulnerable to sleepiness than the sensory-specific subcomponent because the inverted MMN measured at M2 was affected by sleepiness to a lesser degree than the MMN measured at Fz. The polarity reversal of the MMN at the mastoid locations when the nose is used as reference (Alho et al., 1986) has been considered to correspond to the supratemporal source of MMN (Näätänen & Alho, 1995; Paavilainen, Alho, Reinikainen, Sams, Näätänen, 1991). One explanation for the present finding may be that the automatic registration of a stimulus difference is less disturbing for falling asleep in comparison with the initiation of an attentional switch.

The behavioural data indicated that the decline in MMN during sleepiness is accompanied by a markedly impaired awareness of the external environment. This finding suggests that MMN is not completely independent of attention. It is, however, possible to speculate that the impaired awareness of the eliciting stimuli is not the only factor responsible for the attenuation of MMN during sleepiness. Although conscious awareness of the external environment is attenuated during sleepiness, the degree of general cortical activation decreases as well. Paavilainen et al. (1987) suggested that the latter phenomenon may be a more probable reason than the former for their failure to detect MMN during sleep. Two changes in stimulus processing associated with the wake/sleep transition could explain the attenuation of MMN in sleepiness even if MMN were an attention-independent response. Winter et al. (1995) argued that a totally different system is responsible for the processing of stimuli during sleep than during wakefulness and that this transition from the "waking system" to the "sleep system" occurs in sleepiness. It is possible that the decay of the MMN response is characteristic of the "sleep system" because the activation of the brain processes reflected in MMN threatens sleep continuity. This hypothesis was based on the fact that ERPs to the same stimuli are considerably different during wakefulness and sleep. Lang et al. (1995) have proposed that the MMN latency starts to fluctuate strongly during the wake/sleep transition. Such latency jitter would understandably cause a reduction in the averaged MMN. This explanation is consistent with the well-known increased variability in reaction times to target stimuli during sleepiness that was also observed in the present study (for a review, see Dinges & Kribbs, 1991).

The MMN was substantially decreased only in clear sleepiness marked by severely impaired behavioral responsiveness. No attenuation of MMN could be detected in connection with the alert-intermediate transition that was characterised by a moderate impairment in behavioural responsiveness. This observation is understandable because voluntary behavioral responding, contrary to highly automatic stimulus processing, is largely dependent on motivation and attentiveness, which are known to be very sensitive to changes in alertness (see, for example, Dinges & Kribbs, 1991).

P3 during sleepiness

During the waking state, the MMN was followed by a positive wave. The scalp distribution of this positivity was more posterior than the scalp distribution of the usual P3a resembling the topography of the P3b (see Donchin & Coles, 1988). The attenuation of the P3 was the most clearly seen at Pz. Harsh et al. (1994) also reported that a parietally distributed P3 to a deviant tone was much reduced during sleepiness when the subjects were instructed to ignore stimuli. The peak latency of this wave was, however, much later (at about 700 ms) than the positivity of the present study. The attenuation of the P3 to the unattended pitch change during sleepiness suggests that the subjects did not become aware of the changes in the ignored stimulus stream in the sleepy state as likely as in the alert state. This possibility is consistent with the attenuation of MMN because, as suggested by Näätänen (1990), the MMN response may serve as an attentional switch. Moreover, the neural processes reflected in the P3 seemed to attenuate earlier than those reflected in the MMN during the wake-sleep transition. This result is supported by our finding that the large deviant tone elicited a reliable MMN but no parietal P3 during objective sleepiness.

Concluding remarks

The study clearly showed that highly automatic stimulus processing, as reflected by the MMN response, is attenuated during sleepiness but its attenuation seemed to start in a later stage in the wake/sleep transition than that of voluntary behavioural responding. The frontal subcomponent of the MMN response is possibly more vulnerable to sleepiness than the sensory-specific subcomponent.

7 GENERAL DISCUSSION

7.1 Main results

In Study I, an MMN-like deflection occurred as a response to the pitch deviant tone during stage 2 sleep when the stimulus change elicited a K-complex (KC trials). No corresponding response was found during the trials not containing a K-complex (NO KC trials) to the pitch deviation. The same held true for a tone identical with the deviant tone but presented without the intervening standard tones in both the KC and NO KC trials. These findings suggest that a genuine MMN response to the deviant tone was recorded in association with the K-complex.

Study II replicated the occurrence of the MMN-type wave during the KC trials when the stimulus difference was small (1000 /1100 Hz) but not when it was large (1000/2000 Hz). The other differences in the ERPs between the KC and NO KC trials could be seen in the N350 wave to the deviant stimuli, the P210 wave to the large deviant stimulus, and the early positive wave to the standard stimulus that immediately preceded the deviant stimuli (near standard). In all cases, the response was larger in amplitude in the presence than in the absence of the KC response to the deviant tones. The ERPs to the standard stimuli that preceded the near standards (distant standard) showed no difference between the trials containing KC and NO KC responses to the following deviant tone.

Study III showed that P3b-type (REM-P3) and P210 deflections were greater in amplitude during tonic than phasic REM sleep. No reliable MMN-type response was detected either during the tonic or the phasic periods of REM sleep. The REM-P3 wave had a longer latency than the waking P3b wave, but otherwise these waves were alike.

The results of Study IV demonstrated that the MMN response starts to decay even before sleep in sleepiness. The result was the same irrespective of whether sleepiness was determined on the basis of subjective experience or electrophysiological signals. This decrease in the MMN was more pronounced at the Fz than at the right mastoid (M2) location. In addition to the MMN, the

P3 wave also decayed during sleepiness. This phenomenon was the most evident at the Pz location. The attenuation in the MMN response was accompanied by clear impairment of voluntary behavioural responsiveness.

7.2 Mismatch negativity during sleep and sleepiness

The present results showed an MMN-like deflection in two out of the three stimulus changes during stage 2 sleep when a deviant stimulus elicited a K-complex. It was surprising that no MMN-like deflection was recorded for the largest stimulus change. In Section 4.4, it was suggested that one reason for the disappearance of the MMN-like deflection for the largest stimulus change was possibly the enhancement of a P210 wave that may have masked the MMN-like wave. This idea was supported by the finding that the P210 to the large deviant tone significantly increased when a K-complex was elicited. The P210 to the small deviant tone showed no corresponding phenomenon. The use of the mastoid channels would have shed new light on the disappearance of the MMN-like deflection for the largest stimulus change because the MMN component is known to reverse its polarity below the Sylvian fissure (Alho et al., 1986).

An alternative explanation for the disappearance of the MMN-like wave for the largest deviation is naturally that no MMN-like wave occurred. At first glance, this unavoidably seems to mean that the MMN-like deflections for the smaller deviations during the elicitation of the K-complex were observed by chance. There is, however, also another possibility. If the threshold for the activation of the K-complex is lower than that for the activation of the MMN-like deflection, then the K-complex to a stimulus change would not always be preceded by the MMN-like deflection. Instead it would occur only when the sensitivity of the brain to external stimuli reaches a certain level. As mentioned in Section 4.4, the likelihood of K-complex responses was considerably greater for the large than for the small deviant tones. Also in Study I, which showed an MMN-like deflection, the probability for a K-complex was clearly smaller for the deviant tone (22.2%) than for the large deviant tone in Study II. These findings indicate that a more specific brain state was needed for the elicitation of the K-complex to the small stimulus changes than to the large ones. It is possible that the MMN-like deflection could occur only during these specific brain states. On the other hand, the ERPs to the standard tones preceding the K-complexes to the small stimulus changes and preceding the K-complexes to the large stimulus changes indicated no reliable difference in the brain state between these trials, although a tendency towards the anticipated difference could be observed. This finding suggests that the brain state was not markedly different at least 625 ms before the presentation of the small and large deviant tones to which a K-complex occurred.

An observation of interest was that the MMN-like deflection could be seen in the small pitch change minus the near standard tone difference curve during the KC trials in Study II in spite of the absence of a negative shift within

the MMN latency in the ERPs to the small deviant tone *per se*. The reason for the negative shift in the difference curve was a positive wave within the MMN latency range in the ERPs to the near standard (separated from the deviant tone by 625 ms). If one had used the ERPs to the near or distant standard tone, as calculated across all the trials of stage 2 sleep, or the ERPs to the distant standard tone during the KC trials, instead of the ERPs to the near standard tone during the KC trials, no reliable MMN-like deflection would have appeared in the difference curve. One could argue that no MMN-like deflection occurred during the KC trials; instead it was only a positive wave to the near standard tone. It is, however, logical to assume that, without the MMN-like deflection, the ERPs to the small deviant tone would have revealed a larger early positive wave than the ERPs to the near standard tone. This reasoning is based on the fact that the brain responses compared were elicited by the stimuli that occurred near each other and thus the microstate of the brain during which the responses were obtained can be regarded as comparable. This finding emphasises the importance of using brain responses to a standard and deviant tone obtained during a comparable brain state when the occurrence of the MMN response is being examined.

The studies of Campbell at el. (1992) and Loewy et al. (1996) showed an MMN-like deflection during REM sleep. Bastuji et al. (1995) also found a negative wave to a deviant tone of 2000 Hz (p=10%) presented among standard tones of 1000 Hz (p=90%), peaking at the same latency as the MMN-like deflection in the studies by Campbell et al and Loewy et al. This wave was greater than the comparable response to the standard tone. The fact that the ISI was long (on average 1200 ms), however, questions the occurrence of the MMN response in the study of Bastuji et al. (1995). The authors themselves do not mention the MMN; instead they talk about the N1 wave. Study III could not replicate these findings of the MMN response during REM sleep, in spite of the fact that the larger of the two pitch changes used was as large as the pitch change in the three afore-mentioned studies.

The other differences in stimulus parameters also seem to fail to explain the inconsistency of these results. The probability of the standard tone was higher (90%) and the ISI was only somewhat longer (625 ms) in Study III than in the studies of Campbell et al. (40%, 500 ms) and Loewy et al. (80%, 600 ms). This combination of the probability of the deviant tones and the ISI in Study III should facilitate the occurrence of the MMN response, especially as compared with the study of Campbell et al. because the memory trace of the standard tone can be expected to be more persistent in Study III due to the greater numbers of repetitions of the standard tone (Cowan et al., 1993; Imada et al., 1993; Sams et al., 1983). As discussed in Section 5.4, the difference in the elicitation of the MMN response between Study III and the previous studies may result from the enhancement of the P210 wave to the deviant tones which possibly masked the MMN in Study III. The enhancement of the P210 to the deviant tone was not evident in the studies of Campbell et al. (1992) and Loewy et al. (1996). The inconsistency in the occurrence of the MMN-like deflection during REM sleep suggests that this phenomenon requires further

study, as does the occurrence of the MMN-like deflection in connection with the elicitation of K-complexes in stage 2 sleep.

The difficulty to record MMN during sleep is understandable because it already attenuates in sleepiness under optimal stimulus conditions for its elicitation, as shown by Study IV. This finding is consistent with the hypothesis that a gradual transition from the "waking system" responsible for the processing of a stimulus difference to the "sleep system" takes place during sleepiness (Winter et al., 1995). There can be several stages in stimulus processing during which failure can cause the attenuation of the MMN response during sleepiness and its disappearance in sleep. Näätänen (1991) mentions the following three stages that are needed for the elicitation of MMN: sensory analysis of the stimuli, the storing of the output of the sensory analysis, and the comparison of the sensory-memory trace to the current input. The observation that differential processing of standard and deviant tones continues during sleep (Bastuji et al., 1995; Nielsen-Bolhman, et al. 1991; Winter et al., 1995; Studies II, III) suggests that the failure in analysing the physical features of stimuli is not the main reason for the attenuation of the MMN response during sleepiness and sleep. Campbell et al. (1992) proposed that the impairment of the storing stage could be the most critical factor and thus the ISI should be less than 0.5 s to elicit full-amplitude MMN in sleep. Unfortunately, there is no study on the MMN response during sleep in which the ISI would have been shorter than 0.5 s. In Study IV, the MMN was attenuated for the large pitch change (20%) and disappeared for the small pitch change (5%) already in sleepiness before sleep stage 1, even when the ISI was 450 ms. In wakefulness, the maximum ISI for the MMN response has been found to be about 10 s (Böttcher-Gandor & Ullsperger, 1992; Sams et al., 1993). It is unlikely that the storing function would decay so considerably during the alert/sleepy transition that the attenuation of the MMN response could be attributed to an ISI that was too long in Study IV. Thus the present evidence suggests that the main reason for the attenuation of the MMN response in sleepiness and sleep is the impairment of the comparison stage. According to Näätänen (1991) and Näätänen et al. (1993b), the generation of the sensory-specific subcomponent that is responsible for the registration of a stimulus difference is determined by two types of neuronal populations. The computational neuronal populations are responsible for the extraction of information, that is, the registration of a stimulus difference. The activational neuronal populations are responsible for the amplitude of the MMN response. Thus the decrease in the MMN component during sleepiness and sleep does not mean *per se* that a stimulus difference would have remained undetected because it is possible that only the amplifying system is impaired. The positive findings on the MMN response during stage 2 sleep (Study I, II) and REM sleep (Campbell et al., 1992; Loewy et al., 1996) can possibly be inferred as indicating that the amplifying system is dampened during most of the time in sleep, but its activity momentarily returns near its waking time level. In stage 2 sleep, this phenomenon may be indicated by the elicitation of the K-complex when the eliciting stimulus change is not large.

The attenuation of the sensory-specific subcomponent is likely not the first change in the MMN elicitation during the wake/sleep transition. As mentioned in Section 6.4, the frontal subcomponent of the MMN response may be more vulnerable to sleepiness than the sensory-specific subcomponent. This effect may be associated with the fact that especially the activation of the frontal subcomponent interferes with falling asleep since its function has been proposed to be the initiation of an attentional switch to an unattended stimulus change (Näätänen, 1990). Interestingly, Loewy et al. (1996) suggested that one possible reason for an unusually short offset latency of the MMN-like wave during REM sleep would be the deactivation of the frontal subcomponent of the MMN response in this state. This phenomenon may be associated with the fact that the activation of the frontal subcomponent may lead to an orienting response to external events which impairs the recuperation process from waking time activity because sleep becomes fragmented.

The well-documented attenuation of the MMN response in sleepiness and sleep may be considered to support the hypothesis that MMN is not independent of attention. It can, however, not be seen as any definite evidence for this hypothesis because, in sleepiness and sleep, the general cortical activation is reduced simultaneously with the attenuation of the connection to the external environment. This change in the general cortical activation may, as such, cause MMN attenuation. There are, however, also observations suggesting that at times full-amplitude MMN may be elicited in sleep. Study I suggests that, when an MMN response is elicited in stage 2 sleep, its amplitude is not reduced when compared with that in wakefulness. Also in Study II, the amplitude of the MMN-like deflection in stage 2 sleep was comparable with the amplitudes found in wakefulness. Loewy et al. (1996) reported that the MMN response to a large pitch change (100%) in REM sleep was reduced in amplitude as compared with that in wakefulness, but not in the case of a small pitch change (5%). It is likely that at least a part of the attenuation of the MMN response to the large pitch change during REM sleep can be attributed to the occurrence of an N2b wave that overlaps MMN in wakefulness. This view is supported by the fact that, in the study of Loewy et al. (1996), the negativity labelled MMN reached its maximum at Cz in wakefulness. The amplitude of the MMN was not reduced in REM sleep when compared with that in wakefulness at Fz, where the MMN component is known to reach its maximum amplitude. Neither of these findings is convincing, however. In Study II, no MMN-like deflection occurred to the large deviant tone during the KC trials in stage 2 sleep. Secondly, Study III failed to confirm the finding of Loewy et al. (1996) of MMN elicitation during REM sleep.

The attenuation of the MMN during sleepiness and sleep may also be affected by an averaging technique which does not necessarily reveal MMN. As mentioned in Section 6.4, the MMN latency possibly starts to fluctuate strongly during the sleep onset period (Lang et al., 1995). This phenomenon understandably would result in a flattened MMN in an averaged curve. The appearance of the MMN-like deflection during sleep in some studies may be due to exceptionally well-synchronised MMN responses during the selected trials. It is also possible that both spontaneous and stimulus-elicited transient

EEG events interfere with the appearance of MMN during sleep in particular (e.g., Nielsen-Bohlman et al., 1991), because these EEG events are much larger in amplitude during sleep than during wakefulness. This phenomenon would require an unusually high number of trials before the small amplitude MMN could be become detectable in sleep.

All in all, the attenuation of the MMN response seems to start even before actual sleep during the wake/sleep transition. This attenuation possibly occurs so that first the frontal subcomponent and then the sensory-specific subcomponent is attenuated. This phenomenon does not, however, indicate *per se* that the incoming sensory input can not be analysed, stored, or compared with the current input in sleep. What seems to be clear is that the initiation of an attentional switch to a change in the auditory environment is impaired during sleepiness and sleep. Sleep may, however, contain states during which a full-amplitude MMN can be recorded.

7.3 P3b wave during sleep

A new finding of this project was that the P3b-type response occurred more likely during tonic than phasic REM sleep. This result is congruous with that of previous studies suggesting that the attentional resources are less available (Berger & Oswald, 1962; Dement & Wolpert, 1958; Firth & Oswald, 1975; Karacan et al., 1966; Pivik & Foulkes, 1966; Taylor et al., 1985; Weinstein et al., 1988) and behavioural responsiveness to external events is more reduced (Price & Kremen, 1980) during phasic than tonic REM sleep, as pointed out in Section 5.4. The result has at least two implications of importance. It strongly argues against the hypothesis that the brain would be in a state of sensory isolation during REM sleep. This result supports the findings of other recent ERP studies (Bastuji et al., 1995; Niiyama et al., 1994). According to Study III, the susceptibility of the brain to changes in the acoustic environment alternates during REM sleep, being higher during tonic periods, however. This finding shows that not only NREM stage 2 sleep, but also REM sleep contains various microstates during which brain responses to auditory stimuli systematically differ from each other. Earlier, the focus has been on stage 2 sleep when the fluctuation of responsiveness has been examined (Bastien & Campbell, 1992; Niiyama et al., 1995; Ujszászi & Halász, 1986; Studies I, II).

A question of interest is why the P3b-type of wave seems to be easier to detect during (tonic) REM than NREM sleep, as suggested by the present thesis and the studies of Bastuji et al. (1995) and Niiyama et al. (1994). One reason may be that the P3b is overlapped by the K-complex during NREM sleep but not during REM sleep, during which no K-complexes occur. According to Salisbury (1994), it is especially possible to observe the P3b to a large stimulus change during NREM sleep without simultaneous K-complex activation. His interpretation was that the P420 wave following the N350 deflection is a counterpart of the P3b wave on the grounds that the P420 wave has a posterior distribution and it is elicited only by intrusive stimulus changes. He regarded

the N350 wave as equivalent to the waking N2 wave. Another interpretation for this finding could be that the N350-P420 waveform represents a vertex sharp wave (V wave) characteristic of stages 1 and 2 sleep.

Another possible reason for the more promising results concerning the P3b wave during (tonic) REM sleep than during NREM sleep could be that external stimuli have a more direct access to the sleeper's awareness during (tonic) REM sleep. Studies in which REM sleep has not been divided into tonic and phasic periods have shown no reliable differences between REM and stage 2 sleep in terms of the awakening threshold (Poitras et al., 1973; Rechtschaffen et al., 1966), responsiveness to a stimulus (Badia et al., 1984; Burton et al., 1988), or the incorporation of a stimulus into a dream (Burton et al., 1988). Only the ability to recall a stimulus after awakening has been found to be somewhat better for REM sleep than for stage 2 sleep (Lasaga & Lasaga, 1977). The study of Price and Kremen (1980) suggests that a stimulus may have a more open access to awareness during tonic REM sleep than during stage 2 sleep. The authors showed that the behavioural response threshold is lower during tonic REM sleep, but similar during phasic REM sleep, as compared with stage 2 sleep. Bastuji et al. (1995) have presented the absorbing idea that a stimulus must be presented during sleep mentation to elicit a P3b wave during sleep. According to these authors, the P3b response could be a prerequisite of the incorporation of a stimulus into an ongoing dream. This idea agrees with the widely accepted concept that the P3b is associated with the revision of the cognitive model of the environment (Donchin, 1981; Donchin & Coles, 1988). During sleep, the cognitive model of the environment can be considered to be replaced by a dream content and the revision of the cognitive model can be thought to be replaced by the incorporation of a stimulus into the dream content. If the hypothesis of Bastuji et al. (1995) is valid, it is possible that the difference in the occurrence of the P3b between stage 2 and REM sleep could be due to a lower probability of dreaming during stage 2 sleep than during REM sleep. This difference in sleep mentation is suggested by findings showing that dreams are less frequently reported after a person awakens from NREM sleep than after REM sleep (for a review, see Pivik, 1978). Therefore relatively fewer potential moments would exist for the elicitation of the P3b during stage 2 sleep than during REM sleep. The results of Study III suggest, however, that, if the sleeper is strongly immersed in his dream during REM sleep, the likelihood of the P3b occurrence considerably decreases.

The hypothesis that the P3b wave occurs during REM sleep is somewhat confusing when the results of the P3b during sleepiness are considered. The attenuation of the P3b wave during sleepiness has been a consistent finding (Broughton & Aguirre, 1987; Harsh & Badia, 1989; Koshino et al., 1993; Morris et al., 1992). Why would the P3b then occur more likely during tonic REM sleep than during sleepiness? It is clear that the connection with external stimuli is better during drowsiness and stage 1 sleep than during REM sleep when measured by the awakening threshold or behavioural responsiveness. The finding of Harsh et al. (1994) that the disappearance of the P3b during the wake/sleep transition is more closely related to the impairment of behavioural responsiveness than to the characteristics of the EEG may be of importance in

this context. This finding suggests that brain processes reflected in the P3b may strongly interfere with falling asleep because it is impossible to fall asleep if behavioural responsiveness is maintained at the same level as in the alert state. In sleep, the same brain processes are possibly associated with the incorporation of stimuli into the ongoing dream. As pointed out in Section 1.2, the level of behavioural responsiveness is reduced in trials during which a stimulus is incorporated into sleep mentation (Burton et al., 1988). Therefore the elicitation of the P3b wave may be associated with activity that decreases the arousing effect of a stimulus, and in this way the P3b could assist in maintaining sleep in a noisy environment.

7.4 K-complex as an indication of microstate

The present thesis provides some evidence that an early positive wave to a standard tone is augmented when the immediately following deviant tone results in a K-complex. This observation can be interpreted to indicate that the brain momentarily becomes so open to external events that the occurrence of a deviant tone threatens the continuity of sleep. The need to protect sleep is probably reflected in the appearance of the K-complex, which may reflect a brain process of returning to the state during which the arousing effect of external events is more successfully limited. This interpretation is more consistent with the hypothesis that the K-complex is a DR than with the hypothesis that it is an OR (see Section 1.2.2.3). Bastien and Campbell (1994) systematically evaluated whether the K-complex is more comparable to the DR or OR. They found that the amplitude of the evoked K-complex decreased in a series of three consecutive K-complexes to three consecutive stimuli. The amplitude was larger for the first K-complex than for the next two. This decrement occurred when the ISI was 5 and 10 s but not when it was 30 s. Next, the authors assessed whether this decrement was due to the habituation process, which is an essential characteristic of the OR. They found that the K-complex convincingly fulfilled two out of nine criteria of habituation presented by Graham and Hackley (1991). The positive cases showed a decline in the K-complex within a series and an increase in the decrement with shorter ISIs. Six criteria were either difficult to test or there were no data available. The criterion that the decrement should be inversely related to the intensity of a stimulus was not met (Bastien & Campbell, 1992). The reasons for the difficulties in testing some criteria were that the level of arousal fluctuates from moment to moment during sleep and that a K-complex does not occur in each trial. Because this analysis did not provide strong evidence for the habituation of the K-complex, Bastien and Campbell (1994) presented an alternative explanation for the decline of the K-complex in a series of three consecutive K-complexes. The authors assumed that the decline could be a result of refractory processes. In this case, the refractory period would be between 10 and 30 s for the K-complex. In addition, it would vary among the various components of the K-complex, being the shortest for the P900 wave and longest for the N550

wave. In all, the analysis of Bastien and Campbell (1994) can be considered to offer more support to the DR than the OR hypothesis of the K-complex .

The sensitivity with which the elicitation of the K-complex indicates openness of the sleeping brain to external events depends on the distinctiveness of the eliciting stimulus. When the eliciting stimulus is markedly salient and the interval between two consecutive stimuli is long, a K-complex may practically occur in every trial[3]. In this case, the occurrence of the K-complex does not indicate a microstate during which the brain would be exceptionally susceptible to external events. Rather, the absence of the K-complex denotes that the brain is markedly closed in relation to the external environment. In Study II, the small pitch change elicited a K-complex only with a probability of 11.3%. In this case, the occurrence of a K-complex can be interpreted as indicating a moment during which the brain was markedly open to external events. The absence of the K-complex did not, however, reveal a microstate characterised by exceptional isolation from the external environment.

It is possible that the different microstates of stage 2 sleep defined in terms of openness to external events also differ in terms of recuperative value. The sleeping brain has been shown to be the most isolated from the external environment during SWS (see Chapter 1), which has been considered to be the most essential sleep stage for the restorative function of sleep (Horne, 1988). This observation suggests that the recuperative power of sleep and the degree of disconnection of the sleeping brain from external events are related phenomena. The study of Bastien and Campbell (1994) interestingly showed a tendency towards a lower probability of evoked K-complexes during SWS than during stage 2 sleep. This phenomenon was especially true when the ISI was long (10 or 30 s) and the probability of evoked K-complexes was increased when compared with a short ISI (5 s) condition. In other words, the incidence of moments during which the external stimuli threatened sleep continuity tended to be lower for SWS than for stage 2 sleep. It can be hypothesised that moments of stage 2 sleep characterised by the absence of the K-complex to a strong stimulus may be more valuable in terms of restoration than microstates characterised by the presence of the K-complex to the same or weaker stimulus.

All in all, the K-complex is interpreted in the present thesis to indicate the termination of a process during which the brain's susceptibility to external events has increased to a level that threatens sleep continuity under the prevailing stimulus conditions. When soft stimuli are used, the elicitation of the K-complex reveals a microstate during which the brain is exceptionally open to external events. When strong stimuli are employed, the absence of the K-complex denotes a microstate during which the brain is closely isolated from the external environment.

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3 At the 2nd Congress of the World Federation of Sleep Research Societies in the Bahamas in 1995, Sallinen, Kaartinen, and Lyytinen (1995) reported that speech stimuli presented with an intensity of 55 dB elicited a K-complex with a probability of 82.1% during stage 2 sleep.

7.5 Recommendations for future study

Thus far, studies of sleep ERPs have not usually included other measures of stimulus processing that could have been used along with ERPs. The combination of ERPs with other measures could, however, provide additional information about the brain processes reflected in ERPs (see for example Harsh, 1994; Harsh et al., 1994). It is difficult to interpret the ERP waves during sleep by merely examining the effects of manipulations of various stimulus parameters or by comparing their appearance (morphology, topography, latency) to ERP waves of wakefulness. This difficulty is due to the fact that during sleep, ERPs contain deflections that are specific to the state in question and only some of the waves resemble those in ERPs during wakefulness. It is possible that responses with similar functions have different manifestations in ERPs during wakefulness and sleep. Winter et al. (1995) have suggested that a different system is responsible for stimulus processing during sleep than during wakefulness and, further, that the transition from one system to the other occurs during drowsiness. If this assumption is valid, then one can not expect comparable cognitive functions to have identical manifestations in ERPs during sleep and wakefulness. This view contradicts the two-system hypothesis of stimulus processing (Salisbury, 1994) that proposes that ERP waves associated with certain cognitive functions in wakefulness would have the same manifestations in ERPs during sleep. A straightforward way to examine ERP waves associated with stimulus detection would be to record ERPs to stimulus presentations when the detection of these stimuli is determined by either a behavioural or subjective measure. Single ERP trials of the same sleep stage could then be classified according to the detection of the eliciting stimulus as indicated by the selected measure. This procedure could reveal whether stimulus detection during sleep is associated with the occurrence of the ERP responses observed in wakefulness in this context or with some sleep-specific brain response. The finding of Burton et al. (1988) that the probability of a behavioural response to a stimulus is lower when the stimulus is incorporated into a dream suggests that the brain processes associated with the detection of a stimulus during sleep may vary according to the measure by which stimulus detection is evaluated.

Another issue of importance is that ERP studies should be designed to determine whether stimuli differing in terms of personal significance are processed differentially by the brain during sleep and whether ERPs can indicate this type of discrimination. There are a few studies supporting the existence of such a mechanism, which would facilitate arousing from sleep when needed. The widely quoted study of Oswald et al. (1960) claimed that the subject's own name elicits K-complexes with a higher probability than another name in stage 2 sleep. In addition, these authors found that names played forwards more often elicited K-complexes than the same names played backwards. Furthermore, Hoelscher et al. (1981) showed that, in REM sleep, subjects incorporated stimuli with a high personal significance more frequently into their dreams than stimuli with a low personal significance. In addition,

Zung and Wilson (1961), Poitras et al. (1973), and Strauch and Schneider-Düker (1978) observed that the arousal threshold was lower for more meaningful than less meaningful stimuli during sleep. This phenomenon was observed in all the examined stages of sleep (stage 2, SWS, REM). Other attempts have, however, been less successful[4]. McDonald et al. (1975) could not replicate the result of Oswald et al. (1960) which showed a discrimination between one's own name and another name during sleep, as indicated by the K-complex. Moreover, Winter (1995) could find no reliable difference between ERPs to a subject's own name and another name during stage 2 sleep. In drowsiness, a P430 wave was larger to the subject's own name than to another name and therefore suggested that auditory stimuli can be processed at the semantic level in this state. The ERP method may, however, provide a well-controlled procedure with which to examine the functioning of the brain mechanism responsible for semantic discrimination during sleep if something like it exists.

7.6 Conclusions

The present thesis reveals that the ability of the sleeping brain to be in touch with the external environment does not only alter among the traditionally classified macrostates of sleep, but that at least NREM stage 2 sleep, as well as REM sleep, are composed of various microstates that differ in terms of the processing of external events. In light of these observations, it is well-founded to question the accuracy of traditional scoring criteria for sleep when the processing of external events is being examined during sleep. It is possible that the occurrence of such responses as MMN and P3b during sleep may be missed if the fluctuation of responsiveness of the brain to external events within a single sleep stage is not taken into account.

The attenuation of the MMN response during sleepiness shows that, not only voluntary and conscious, but also highly involuntary and preconscious auditory information processing is affected by a decrease in alertness. In spite of these changes in highly automatic stimulus processing during sleepiness, subjects retain their ability to respond behaviourally to auditory targets even though reaction times become slower. This finding suggests that sleepiness-related impairments in stimulus processing mainly occur simultaneously in the automatic and controlled processing modes. Some evidence has indicated that changes in the controlled processing mode would, however, appear in an earlier phase in the wake/sleep transition than in the automatic processing mode. All in all, the changes in ERPs to a deviant tone during sleepiness, as observed in the present study, support the concept of sleepiness as a smooth transition between wakefulness and sleep (Pivik, 1991).

4 At the 2nd Congress of the World Federation of Sleep Research Societies in the Bahamas in 1995, Sallinen, Kaartinen, and Lyytinen (1995) reported that ERPs are not reliably different for the subject's own name played forwards vs. backwards during NREM or REM sleep. The same held true for the probability of the K-complex during stage 2 sleep. Only hear rate responses showed some evidence of discrimination between the speech stimuli.

YHTEENVETO

Tutkimuksen yleisenä tavoitteena oli selvittää monotonisessa äänisarjassa esiintyvän fysikaalisen muutoksen käsittelyä aivoissa unen ja uneliaisuuden aikana. Erityisenä kiinnostuksen kohteena oli, esiintyykö univaiheiden sisällä ns. mikrotiloja, jotka systemaattisesti eroavat toisistaan ulkoisten ärsykkeiden käsittelyn suhteen. Uneliaisuus sisällytettiin tutkimukseen, koska pyrkimyksenä oli selvittää ärsykkeen automaattisessa käsittelyssä tapahtuvia muutoksia jo ennen varsinaista unta. Menetelmänä käytettiin aivosähkökäyrään eli EEG:hen perustuvaa aivojen herätevaste (event-related brain potentials, ERPs) menetelmää, jossa EEG:ssä esiintyvät ärsykesidonnaiset jännitemuutokset erotetaan spontaaneista jännitemuutoksista keskiarvoistamalla kymmeniä tai satoja yksittäisiä, kriittisten ärsykkeiden ympäriltä kerättyjä EEG-pätkiä.

Ensimmäisessä osatutkimuksessa pyrkimyksenä oli selvittää poikkeavuusnegatiivisuudeksi (mismatch negativity, MMN) nimetyn aivojen herätevasteen esiintymistä kevyessä S2-unessa. MMN edustaa suuressa määrin tai kokonaan tarkkaavaisuudesta riippumatonta ärsyke-eron rekisteröimistä ja tarkkaavaisuuden kääntämisen aloittamista kohti ärsykemuutosta. Tavoitteena oli erityisesti selvittää, liittyykö MMN:n esiintyminen S2-unessa K-kompleksiksi nimetyn suuriamplitudisen ja monivaiheisen EEG-vasteen laukeamiseen poikkeavaan ääneen. Aiemmissa tutkimuksissa S2-unta ei ole jaoteltu vastaavin perustein. MMN:n kaltainen vaste oli havaittavissa S2-unessa, mutta vain silloin, kun ärsykepoikkeama laukaisi myös K-kompleksin, joka on myöhäisempi reaktio kuin MMN. Vastaavaa jännitemuutosta ei voitu havaita, kun monotonisen äänisarjan muodostaneet standardiäänet poistettiin devianttiäänien ympäriltä. Tämä tulos viittaa siihen, että MMN:n kaltainen vaste todella oli MMN.

Toisessa osatutkimuksessa pyrittiin replikoimaan MMN:n kaltaisen jännitemuutoksen esiintyminen S2-unessa K-kompleksin laukeamisen yhteydessä. Lisäksi selvitettiin, mitä muita spesifisti K-kompleksin laukeamiseen liittyviä tapahtumia voidaan aivojen herätevasteissa havaita *ennen* K-kompleksin alkulatenssia. Tulokset osoittivat, että MMN:n kaltaisen vasteen esiintyminen K-kompleksin laukeamisen yhteydessä voitiin havaita, kun laukaiseva ärsyke-ero

oli pieni (10 %). Suuri ärsyke-ero (100 %) ei tuottanut merkitsevää MMN:n kaltaista vastetta K-kompleksin laukeamisen yhteydessä. MMN:n kaltaisen vasteen latenssin jälkeen esiintyvä N350 vaste kasvoi johdonmukaisesti, kun joko pieni tai suuri ärsykepoikkeama laukaisi K-kompleksin. Tämä on yhdenmukainen tulos aiempien havaintojen kanssa. MMN:n kaltaisen ja N350 vasteen välissä esiintyvä P210 aalto kasvoi myös K-kompleksin laukeamisen yhteydessä, mutta vain silloin, kun ärsyke-ero oli suuri. Aiemmista tutkimuksista poiketen aivojen herätevasteita mitattiin myös *ennen* poikkeavia ääniä esiintyneisiin standardiääniin. Aikainen positiivinen vaste standardiääneen kasvoi merkitsevästi, kun välittömästi (625 ms) sen jälkeen esiintynyt poikkeava ääni laukaisi K-kompleksin. Tätä ilmiötä ei voitu havaita, kun aika stanradi- ja devianttiäänen välillä kaksinkertaistui.

Kolmannessa osatutkimuksessa tutkittiin P3b:ksi nimetyn aivojen herätevasteen esiintymistä REM-unen (rapid eye movement sleep) aikana. P3b heijastaa ärsykkeen tunnistamiseen ja ympäristöstä muodostuneen kognitiivisen mallin päivittämiseen liittyviä prosesseja aivoissa. Erityisen kiinnostuksen kohteena oli, esiintyykö P3b-tyyppinen vaste nimenomaan toonisessa REM-unen alavaiheessa, jolloin nukkuja on vähemmän uppoutunut näkemiinsä uniin ja hän on valmiimpi behavioraalisesti reagoimaan ääniin verrattuna faasiseen REM-uneen. Aiemmissa vastaavissa tutkimuksissa REM-unta ei ole jaoteltu osavaiheisiin. Tulokset tukivat hypoteesia P3b-tyyppisen vasteen esiintymisestä nimenomaan toonisessa REM unessa. MMN:n kaltaista vastetta ei esiintynyt REM unen aikana, mikä on ristiriidassa aiempien havaintojen kanssa. P3b-tyyppisen jännitemuutoksen lisäksi P210 vaste oli suurempi toonisen REM-unen kuin faasisen REM-unen aikana.

Neljännessä osatutkimuksessa selvitettiin MMN:n ja sitä seuraavan P3-vasteen esiintymistä uneliaisuuden aikana. P3 edustaa tarkkaavaisuuden kääntymistä tarkkaavaisuuden ulkopuolella esiintyneeseen ärsykkeeseen, mikä johtaa ärsykkeen havaitsemiseen. Aiemmista vastaavista tutkimuksista poiketen ärsykeolosuhteet olivat optimaaliset MMN syntymiselle. Toiseksi uneliaisuus määriteltiin erikseen elektrofysiologisten tapahtumien ja subjektiivisen kokemuksen perusteella. Aiemmissa tutkimuksissa on käytetty vain elektrofysiologista määrittelyä. Lisäksi mittausjaksojen aikana selvitettiin tutkittavien suoriutumista reaktioaikatehtävässä. Aiemmissa tutkimuksissa tutkittavat ovat vain pyrkineet nukahtamaan MMN:n rekisteröinnin aikana. Tulokset osoittivat sekä MMN:n että P3:n heikkenevän uneliaisuuden voimistuessa. MMN:n heikkeneminen oli havaittavissa erityisesti frontaali- ja sentraalikanavalla, mutta ei niinkään Sylvian uurteen alapuolisella kanavalla. Tutkittavien suoriutuminen reaktioaikatehtävässä heikkeni selvästi uneliaisuuden voimistuessa. Tämän voluntaarisen reagoinnin voitiin havaita heikkenevän jo varsin vähäisen vireyden laskun yhteydessä, jolloin MMN:ssä ja P3:ssa ei vielä esiintynyt muutoksia. Toisaalta tutkittavat kykenivät behavioraalisesti reagoimaan lähes kaikkiin tarkattuun korvaan esitettyihin ääniin vielä silloinkin, kun vireyden lasku johti MMN:n ja P3:n voimakkaaseen heikkenemiseen tarkkaamattomaan korvaan esitettyihin ääniin.

Kaiken kaikkiaan osatutkimukset viittaavat siihen, että MMN:n edustama ärsyke-eron prosessointi heikkenee jo uneliaisuuden aikana, mutta jossain

unen mikrotiloissa sen laukeaminen saattaa olla mahdollista. Näille mikrotiloille näyttäisi olevan tyypillistä se, että niiden aikana aivot ovat poikkeuksellisen "avoimet" ulkoisille tapahtumille. Erityisesti MMN:n heijastama tarkkaavaisuuden kääntymisen aloittaminen ärsykemuutokseen näyttäisi olevan herkkä vireyden laskulle. Sen sijaan ärsyke-eron rekisteröiminen mahdollisesti jatkuu muuttumattomana hieman pidempään vireyden alkaessa laskea. P3b:n edustaman ärsykkeen kognitiivisen käsittelyn esiintyminen puolestaan näyttäsi olevan yhteydessä siihen, kuinka paljon rajallisista tarkkaavaisuusresursseistamme on sidottu nähtyihin uniin. P3b:n syntyminen on todennäköisempää toonisen REM-unen aikana, jolloin nukkuja on vähemmän uppoutunut uniinsa.

Osatutkimusten perusteella voidaan tehdä kaksi yleistä johtopäätöstä: a) traditionaalisesti luokitellut univaiheet sisältävät mikrotiloja/alavaiheita, jotka systemaattisesti eroavat toisistaan ulkoisten tapahtumien käsittelyn suhteen ja b) unelle tyypillistä vaimenemista MMN:n heijastamassa tiedonkäsittelyssä voidaan havaita jo uneliaisuuden aikana, joskin ärsykepoikkeama mahdollisesti laukaisee MMN:n joissain unen mikrotiloissa.

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