Event-related Potential Measures of Stimulus Deviance During Natural Sleep

by

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Abstract

An occasional "deviant" stimulus presented in a train of frequent homogeneous "standard" stimuli elicits a negativity, called the "mismatch negativity" (MMN), in the human auditory evoked potential (AEP). The MMN occurs at approximately 100-300 ms after stimulus onset. In awake and alert subjects, the MMN appears to be elicited regardless of the level of attention, conscious awareness, or task demands. It could however be argued that awake and alert subjects always have at least partial awareness of the stimulus even during conditions of seeming inattention. The purpose of the present thesis was to examine the attentional independence of the MMN by recording event-related potentials (ERP) to different types of stimulus change or "deviance" during natural sleep. In three separate experiments, stimulus deviations involving frequency, duration, and intensity were examined. Sleep may be the time when subjects are least conscious of their external environment. In experiment 1, two "oddball" stimulus conditions involving auditory frequency deviance were presented to eight subjects. In the "large deviance" condition, 2000 Hz "deviant" tones (probability =.20) were presented with 1000 Hz "standard" tones (p=.80). In the "small deviance" condition, 1050 Hz deviants were used. Stimuli were presented at a constant inter-stimulus interval (ISI) of 600 ms. Both stimulus conditions were presented during wakefulness, as subjects read a book, and during Stage 2, REM, and slow wave sleep (SWS). A MMN was elicited in the 100-200 ms latency range by large deviants during wakefulness. Small deviants also elicited a MMN appearing in the 150-200 ms range. In REM sleep, a smaller amplitude MMN, peaking between 100-150 ms, was observed for

large deviants. An MMN of similar amplitude to that seen in waking was elicited by small deviants at approximately 100-150 ms. No MMN was observed in the non-REM (NREM) sleep stages.

In experiment 2, two stimulus conditions involving deviations in stimulus duration were presented to eight subjects. In the "increment deviance" condition, 150 ms deviant tones (p=.10) were presented with 100 ms standards (p=.90). In the "decrement deviance" condition, 50 ms deviant tones (p=.10) were used. Once again, stimuli were presented at a constant ISI of 600 ms. Both conditions were presented during wakefulness (reading), and sleep stages 2, REM and SWS. In wakefulness, a MMN was observed for the increment deviants in the 150-300 ms interval. The decrement deviants elicited a MMN that occurred in the 150-250 ms interval. No statistically significant MMN-like negativities were elicited in any sleep stage by either type of deviant. In REM sleep, a small negativity appeared however in the 250-300 ms latency range for increments and in the 150-200 ms range for decrements. The latencies of these waves corresponded highly with the latencies of the MMNs elicited in wakefulness by the same stimuli. In addition, these negativities conformed to the scalp distribution for the MMN described in the literature. Consistent with the first study, no MMN-like wave was evident in any NREM sleep stage.

In experiment 3, stimuli involving changes in auditory intensity were presented to seven subjects during a waking reading condition, Stage 2 and REM sleep. Within the same stimulus block, 80 dB "increment deviants" and 60 dB "decrement deviants" were presented with 70 dB standard tones. The ISI was again set at 600 ms. During the waking condition, the increment deviants elicited a long-lasting fronto-central negativity. A long-lasting

negativity was also evident for decrement deviants but its amplitude was much attenuated. In REM sleep, a long latency peak was still evident at approximately 325 ms, but the earlier peak seen in waking, was not apparent. The scalp distribution of this late negative peak was consistent with that of the MMN. A large, late negativity, lasting from 300-450 ms, was also observed in Stage 2, but its scalp distribution did not resemble that of the MMN.

The results of the three studies indicated that the MMN to frequency deviance is preserved during REM sleep, and the MMN to duration deviance may also be present in REM sleep, but is much attenuated relative to wakefulness. The detection of intensity deviance persists in REM sleep, but it is uncertain whether this is due to a true mismatch process or a deviant-related negativity specific to the REM sleep state. No MMN-like activity could be recorded to any type of stimulus deviance during NREM sleep.

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Curriculum Studorium

Derek Loewy was born in Moncton, New Brunswick on May 9th, 1963. He was raised in Ottawa and completed his Bachelors Degree in Psychology at Carleton University in the spring of 1987. He then completed his Masters Degree in Psychology at Carleton University in the spring of 1989. In 1991, he obtained certification as a Registered Polysomnographic Technologist (R.Psg.T.). During his academic training he was active in the publication of articles and the presentation of abstracts at the meetings of learned societies.

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TABLE OF CONTENTS

Organizational Note

This dissertation consists of five chapters. Chapter 1 introduces the thesis by reviewing the literature and developing the rationale for the studies to follow. Chapters 2, 3 and 4 represent three separate experiments. These are presented in article format. As such, each study consisits of separate Introduction, Methods, Results and Discussion sections. Each study is preceded by a single page which discusses that rationale for that experiment. Chapter 5 presents a general discussion and integration of the findings of the three studies. The format of each article conforms to that specified by the journal to which it has (or will be) sent. Chapter 2 is "in press" in the journal Electroencephalography and Clinical Neurophysiology (Accepted February, 1996). Chapters 3 and 4 will be submitted to the same journal. References are presented at the end of the thesis, rather than at the end of each chapter, to avoid redundancy. In Appendix A, a brief technical article is presented. This paper is under review by the Journal of Psychophysiology.

Chapter 1

Introduction

The recording and measurement of the brain's electrical activity as a means of assessing consciousness and arousal states in humans has a long history (Berger, 1929; Loomis, Harvey, & Hobart, 1935, 1936; Davis, Davis, Loomis, Harvey, & Hobart, 1939). One such approach involves the recording of "evoked potentials" (EPs). EPs are brain microelectrical events that are time-locked to an evoking stimulus (or psychological event) and reflect the summated electrical potential activity of neuronal structures associated with the processing of the stimulus. They have been used extensively to investigate the neurophysiological mechanisms of human information processing (Davis et al., 1939; Sutton, Braren, Zubin, & John, 1965; Hillyard, Hink, Schwent, & Picton, 1973; Näätänen, Simpson, & Loveless, 1982).

The evoked potential "signal" is embedded in the "noise" of the ongoing EEG and must therefore be extracted from the background activity by presenting many stimulus repetitions and using the techniques of averaging. The average evoked response consists of a sequence of positive and negative deflections or components[1], each differing with respect to peak amplitude, measured in microvolts (μV), latency from stimulus onset, measured in

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[1] In the present document the term 'component' will be used interchangeably with the terms 'peak' and 'deflection' of an auditory evoked potential. This usage is consistent with much of the literature. It should be noted however that Naatanen and Picton (1987) defined a component as "...the contribution to the recorded waveform of a particular generator process, such as the activation of a localized area of cerebral cortex by a specific pattern of input....Whereas the peaks and deflections of an EP can be usually inferred only from the results of the experimental manipulation".

milliseconds (ms), and voltage distribution on the scalp. EP components are generally classified as either "exogenous" or "endogenous" (Sutton et al., 1965). Exogenous components usually occur soon after stimulus onset and are affected by the physical characteristics of the eliciting stimulus. They are stable "obligatory" responses of the nervous system that are elicited, regardless of the level of attention or conscious awareness of the subject. Endogenous components usually occur later and are influenced by the internal psychological state of the subject. They therefore show greater variability across different attentional and consciousness states. Due to their association with psychological events, the late components are also referred to as "event-related potentials" (ERPs). The distinction between the exogenous and endogenous components has heuristic value but is not clear-cut. Picton and Hillyard (1974) suggested that a continuum existed between the wholly exogenous and wholly endogenous components. Recently, Picton, Lins, and Scherg (1995) stated that exogenous components are "evoked" by an external stimulus, whereas endogenous components are "emitted" by the brain when it makes a decision or initiates a response.

The present thesis will investigate auditory evoked potentials (AEPs). They have been divided into the early (1-10 ms), middle (10-50 ms), and late components (i.e., beyond 50-800 ms). The early components are primarily exogenous, originating in "far-field" peripheral (auditory nerve) and brainstem sites. The later components are primarily endogenous. Their intra-cranial origins remain largely unknown although present evidence suggests they are probably cortically-generated in regions in and around the auditory cortex and perhaps the frontal lobe.

ERPs have often been recorded to examine the effects of the attentional/conscious

state on the processing of stimulus deviance. The most relevant ERP candidates for study are obviously those that are affected by the subject's level of attention (i.e., the late ERPs). It has been shown for example, that the brainstem auditory EPs are relatively unaffected by sleep (Amadeo & Shagass, 1973; Osterhammel, Shallop, & Terkildsen, 1985; Campbell & Bartoli, 1986; Bastuji, Garcia-Larrea, Bertrand, & Mauguière, 1988).

Late Components of the Auditory Evoked Potential

The first of the late components of the auditory ERP is generally considered to be a positive deflection peaking at approximately 50-75 ms and labelled "P1". P1 is maximal over central areas of the scalp and evidence suggests it originates in the primary auditory cortex (Goff, Matsumiya, Allison, & Goff, 1977). The psychological relevance of P1 has however not been precisely determined (Näätänen, 1992). P1 is followed by complex of waveforms labelled "N1-P2-N2". N1 is a negative wave with a vertex maximal amplitude that typically occurs approximately 80-100 ms after stimulus onset. The N1 response is elicited by abrupt changes in the level of physical energy impinging on the sensory receptors. N1 may therefore occur in response either a change in acoustic energy from some immediately preceding stable level (i.e., from silence to sound or from sound to silence) or to an auditory stimulus change (i.e., change from some previously presented stimulus). N1 appears to be more sensitive to the former type. This was demonstrated by Näätänen, Paavilainen, Alho, Reinikainen, and Sams (1987a) who found that an occasional deviant tone elicited a larger N1 than frequent standards of lower intensity. However, if the deviant stimulus was lower in intensity than the standards, it elicited a smaller N1. Thus the

amplitude of N1 was influenced more by the characteristics of the stimulus itself than by the change it represented from the preceding stimulus.

N1 is not a unitary response. Näätänen and Picton (1987) proposed that there are at least three "true" N1 subcomponents, overlapping at approximately 100 ms, that comprise the vertex N1 response. The first is a contralaterally larger fronto-central negative wave, peaking at approximately 100 ms, that is probably generated in the supratemporal plane of the auditory cortex. The second is a midtemporal biphasic wave with a positive component at 100 ms and a negative component at 150 ms which may be generated in the supratemporal gyrus. The third element is a non-specific negative wave of unknown origin occurring at 100 ms with a maximal amplitude at the vertex. Giard, Perrin, and Echallier (1990) showed that the supratemporal N1 is accompanied by an additional frontal component occurring at a similar latency. The authors suggested that this component may be related to mechanisms associated with conscious perception of the stimulus.

The latency of N1 is relatively stable. The amplitude increases however for increasing magnitudes of physical stimulus change. When stimuli are presented repeatedly, particularly at fast rates, the amplitude of N1 decreases. It is not entirely certain whether this response decrement is due to refractoriness of the receptors or habituation. Näätänen and Picton (1987) argued that it is probably due to refractoriness because dishabituation could not be demonstrated. They suggested that the refractoriness of the supratemporal component is sensory-specific, whereas the refractoriness of the non-specific component is associated with decreased time uncertainty of the eliciting stimulus.

There is some controversy concerning the effects of selective attention on N1.

Hillyard et al. (1973) first noted that N1 amplitude was greater for attended "target" stimuli than for ignored stimuli. It remains uncertain whether or not this effect is due to an attentional modulation of exogenous N1 generators or a reflection of an endogenous attention effect. Näätänen and colleagues (Näätänen & Picton, 1987; Näätänen & Alho, 1995) have argued that most attention related effects on N1 are due to the endogenous "processing negativity" (PN). PN is a negative displacement in the ERP that is elicited by stimuli presented to an attended channel. PN may commence as early as 100 ms and thus may overlap and summate with N1 thus enhancing its amplitude for attended stimuli.

N1 is followed by P2, a positive wave occurring approximately 175-225 ms after stimulus onset. Very little has been reported concerning the functional significance of P2. The locus of origin of the P2 appears to be the supratemporal auditory cortex and it may be related to the supratemporal component of the N1 (Vaughan, Ritter, & Simson, 1980). N1 and P2 frequently show covariation and may therefore share some functional relationship. The two waves can be dissociated experimentally however and their scalp distributions are different (Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991). Components whose scalp distributions are different must have different intra-cranial generators (Picton et al., 1995). It is probable therefore that they represent distinct cerebral processes.

The N1-P2 complex is followed by a negative deflection, N2, occurring between 250-300 ms. N2 shows a maximal fronto-central distribution. A wide variety of N2-like waves have been reported. N2 has often been observed to be related to the detection of stimulus change or deviance (Snyder & Hillyard, 1976). An occasional deviant stimulus elicits a much larger N2 response than does a sequence of repetitive homogeneous stimuli. The N2 is

typically recorded using an "oddball" paradigm in which a number of infrequent "deviant" stimuli are interspersed among a series of frequent "standards". Squires, Squires, and Hillyard (1975) employed an oddball condition and found that N2 was greater for the rare stimuli than for frequent stimuli, regardless of task demands. Similar findings were obtained by Näätänen, Gaillard, and Mantysalo (1978) who recorded ERP responses to slight pitch and intensity deviant stimuli. They also found however that this effect occurred whether or not the subject was instructed to attend to the stimulus. That is, N2 amplitude was the same for attended and non-attended deviants. They concluded therefore that N2 occurred automatically, regardless of the meaningfulness of the stimulus or the level of attention of the subject. Thus, N2 may be related to the Orienting Reflex (Sokolov, 1975).

The functional significance of N2 was later refined by Näätänen et al. (1982). They presented large blocks of auditory stimuli involving either slight (small deviant) or wide (large deviant) frequency changes. Standards were 1004 Hz ($p=.95$) tones. Small deviants were 978 Hz or 1034 Hz ($p=.02$ each) and large deviants were 1404 Hz ($p=.01$). Stimuli were presented at a relatively rapid rate (768 ms) during both ignore and attend conditions. Consistent with previous findings, N2 amplitudes for the small deviants were similar across conditions whether or not they were attended. In contrast, a double-peaked negativity was observed in the N2 latency range for the large deviants when subjects were instructed to detect them. The first peak had a shorter latency and overlapped with the N1. The second peak was a sharp negativity that occurred slightly later. The authors thus divided the N2 into two distinct subcomponents. The first, termed the "N2a", was elicited by a deviation in the physical properties of an infrequent stimulus and a background of frequent homogeneous

stimuli. Since N2a was affected by the physical properties of the deviant stimulus and was independent of subjective, psychological factors, it appeared to meet the criteria of an "exogenous" component. Because N2a is elicited by a deviant (or mismatch) stimulus it has been labelled the "mismatch negativity" (MMN). A MMN response has since been observed in a variety of deviant stimulus conditions. (The MMN is described in greater detail in a later section) . The second component was an endogenous negativity, "N2b". N2b followed N2a when the deviant stimuli were attended and detected. N2b could nevertheless be elicited by deviants in ignore conditions if they were widely different from the standards (Näätänen et al., 1982; Alho, Lavikainen, Reinikainen, Sams, & Näätänen, 1990; Novak, Ritter, Vaughan, & Wiznitzer, 1990). It may be that strongly deviant stimuli are intrusive and are difficult to completely ignore even when attention is being directed elsewhere.

The N2 wave of the AEP is followed by a late positive wave, "P3". The P3 or P300 is maximal over centro-parietal areas of the scalp and peaks between 330-500 ms during relatively easy discrimination tasks (Sutton et al., 1965). P3 is predominantly endogenous, in that its amplitude is strongly related to the subjective relevance of the eliciting stimulus and to its probability of occurrence. A large P3 is elicited by infrequent and psychologically relevant deviant stimuli that are actively detected. In oddball conditions, P3 will be elicited by rare, detected "target" deviants but not by frequently-occurring detected standards. The P3 wave consists of an early subcomponent called the "P3a" (as distinguished from the main P3 or "P3b"). The P3a has a smaller amplitude and a more anterior distribution than the P3. It also comprises the early portion of the P3 complex (Squires et al., 1975). There is a very strong association between P3a and the preceding

N2b. In attend conditions, N2b is followed by P3a (Näätänen et al., 1982; Loveless, 1986). Sams, Paavilainen, Alho, and Näätänen (1985) noted however that, as in the case of the N2b, a small amplitude P3a may be elicited in ignore conditions. The authors explained this finding by relating it to experiences reported by subjects of occasionally becoming "aware" of the deviant presentations while they were engaged in a distracting task (i.e., reading). Thus the P3a may be a reflection of this awareness of the deviant in the absence of active attention toward it. This effect is more probable for widely deviant stimuli because of their intrusiveness.

Evoked Potentials During Sleep

In awake subjects, it is difficult to determine, precisely, the effects of attention on the component structure of the AEP. Even in conditions of highly focused attention, it may be difficult, if not impossible, for subjects to remain completely unaware of "to-be-ignored" input. Studies of waking selective attention have shown that the AEP in ignore conditions may reveal some measure of processing of the "ignored" stimulus. On example of this effect is the appearance of an occasional, small amplitude N2b-P3a complex to task-irrelevant but widely deviant stimuli (Näätänen et al., 1982; Sams, Paavilainen et al., 1985). One means of exploring the relationship between stimulus deviance and level of processing is to examine AEP components recorded in sleep.

Sleep is probably the state when we are least aware of the external environment. Davis et al. (1939) were the first to systematically record auditory evoked potentials in sleeping subjects. They noted changes in the ongoing sleep EEG which corresponded to the

presentation of external stimuli thus demonstrating that this information was being processed by the sleeping brain. This activity probably reflected the elicitation of large, late complex of waves (N350-N550-P900) seen in NREM sleep called the "K-Complex" (Bastien & Campbell, 1992, discussed later). Since that time, much research has been conducted concerning how information is processed during sleep.

It appears that brainstem AEPs, reflecting the activity of the auditory nerve and brainstem relay centres, are relatively unaffected by sleep (Amadeo & Shagass, 1973; Osterhammel et al., 1985; Campbell & Bartoli, 1986; Bastuji et al., 1988). There may be some latency changes in these components, associated with decreased core body temperature (Bastuji et al., 1988). The brainstem responses remain constant however regardless of stimulus intensity or rate of presentation (Campbell & Bartoli, 1986; Deacon-Elliott, Bell, & Campbell, 1987). The midlatency components have been reported to be altered by sleep in some studies (Linden, Campbell, Hamel, & Picton, 1985; Erwin & Buchwald, 1986) but not in others (Mendel & Goldstein, 1969; Picton & Hillyard, 1974; Hackley, Woldorff, & Hillyard, 1990). Campbell, Bell and Bastien (1992) claimed that these discrepancies may be due to the use of different filter settings or by the use of different stimulus presentation rates. They found that middle components were attenuated in sleep with fast rates of presentation (i.e., 16 clicks per second), but were relatively unaffected with slower rates of presentation (i.e., every 2 to 8 per second).

The most dramatic effects of sleep on the AEP begin to occur beyond 50 ms after stimulus onset. There are marked changes in the P1-N1-P2 "vertex complex" of waves. In the waking state, selective attention to a channel results in the processing negativity

(discussed above) which may overlap with and summate to the P1-N1-P2 components making all three more negative. The summating effects of this negative attentional wave increase the amplitude of the negative wave, N1, but reduce the amplitudes of the positive waves, P1 and P2, relative to the pre-stimulus baseline. Alho, Sams, Paavilainen, and Näätänen (1986) noted that the processing negativity, at least the early portion, is activated even in to-be-ignored channels. Awake and alert subjects are never able to completely ignore their external environment. As such, subjects are always at least partially conscious of the stimulus. The period of time during which subjects are least conscious is during sleep. The onset of sleep results in a gradual decrement in the amplitude of N1, while P1 and P2 amplitudes are enhanced (Ogilvie, Simons, Kuderian, MacDonald, & Rustenburg, 1992; Harsh, Voss, Hull, Schrepfer, & Badia, 1994; De Lugt, Loewy, & Campbell, in press). This effect may be due, in part, to the removal of the negative influence of the waking PN associated with sleep onset.

There is some controversy concerning the effects of sleep on the amplitude of P1. Osterhammel et al. (1985) and Erwin and Buchwald (1986) found that P1 amplitude decreased in non-REM sleep. Nielsen-Bohlman, Knight, Woods, and Woodward (1991) reported that P1 amplitude did not change during initial Stage 2 sleep but later decreased in Stages 3 and 4. Other studies have reported an increase in P1 amplitude (Paavilainen, Cammann, Alho, Reinikainen, Sams, & Näätänen, 1987; Williams, Tepas, & Morlock, 1962) or a decrease in P1-N1 peak-to-peak amplitude (Anch, 1977; Kevanishvili & von

Specht, 1979)[2] in NREM sleep. Still, others have reported relatively little change in amplitude (Weitzman & Kremen, 1965; Fruhstorfer & Bergstrom, 1969). Campbell et al. (1992) accounted for these discrepancies by noting methodological differences, particularly the choice of filter settings. For example, many laboratories have employed relatively short amplifier time constants. Slow waves, such as the processing negativity would therefore be attenuated by the low filter setting. An artificially small P1 would thus be observed during wakefulness. During sleep, the processing negativity may be markedly attenuated. Since its overlapping and summating effects on P1 are removed, P1 would therefore appear to be larger in sleep.

The majority of studies have found that N1 decreases in amplitude in NREM sleep (Fruhstorfer & Bergstrom, 1969; Kevanishvili & von Specht, 1979; Paavilainen et al., 1987; Nielsen-Bohlman et al., 1991; Campbell et al., 1992), although some (using peak-to peak measures) have found that it is relatively unaffected (Williams et al., 1962; Weitzman & Kremen, 1964). Ogilvie et al. (1991) and Harsh et al. (1994) reported a gradual reduction in N1 amplitude in Stage 1 sleep and its eventual removal as the subject progressed into Stage 2 sleep. The effects of sleep onset on the amplitude of N1 may be related to the rate of stimulus presentation. De Lugt, Loewy, and Campbell (in press) demonstrated that, at a slow presentation rate (ISI=1000 ms), N1 amplitude was at or near the waking level in

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[2] Early studies often determined the amplitude of ERP waves by performing peak-to-peak measures. The drawback of this approach is that it becomes difficult to attribute amplitude differences to a change in one component or the other, or both. When negative and positive components are overlapped by a slow wave, such as the processing negativity, while peak-to-peak measurement may not change, the baseline-to-peak measure for both components will change. Thus if P1 increases in amplitude (relative to baseline) and N1 decreases in amplitude, to the same extent, during sleep, the P1-N1 peak-to-peak amplitude measure will not vary. Most recent studies employed baseline-to-peak measurements performed on each component separately.

Stage 1 sleep. At a faster rate (ISI=600 ms) however , N1 amplitude attenuated to near baseline in Stage 1 sleep (De Lugt, Loewy, & Campbell, 1995). Stimuli that are presented slowly are probably more difficult to ignore. Schwent et al. (1976) indicated that during studies of selective attention, N1 amplitude did not vary between attend and ignore conditions if stimuli were presented slowly. The latency of N1 at sleep onset has been found to increase slightly by some (Campbell et al., 1992) or be unaffected by others (Weitzman & Kremen, 1964).

The effects of sleep on P2 are much more variable. Some have reported a decline in P2 amplitude in NREM sleep (Williams et al., 1962; Williams, Morlock, Morlock, & Lubin, 1964; Fruhstorfer & Bergstrom, 1969), while others have reported that P2 amplitude increases with the onset of NREM sleep and declines thereafter (Kevanishvili & von Specht, 1979; Campbell et al., 1992; Harsh et al., 1994). The findings of reduced P2 amplitude in at sleep onset reported by the earlier studies may have been confounded by the problems associated with the use of peak-to-peak measurements discussed earlier. A smaller P2 might be observed if it was measured in relation to an N1 peak which markedly declines in sleep. Campbell, McGarry, and Bell (1988) reported that N1 amplitude is reduced to baseline and P2 increases in amplitude in NREM sleep, regardless of stimulus intensity. Still other researchers have found relatively no change in P2 amplitude with NREM sleep (Weitzman & Kremen, 1965). Again, the rate of stimulus presentation may serve as an interacting variable (De Lugt et al., in press). P2 latency is also variable, suggesting that it either increased in NREM sleep (Kevanishvili & von Specht, 1979), decreased with approaching sleep Fruhstorfer & Bergstrom, 1969), or was unchanged (Williams et al., 1962, Williams et al.,

1964; Weitzman & Kremen, 1965).

The effects of general anesthesia on the AEP resemble those of sleep onset. N1 amplitude was found to decline with sufentanil anesthesia (Plourde, Joffe, Villemure, & Trahen, 1993) and be abolished with thiopental/isoflurane anesthesia (Plourde & Picton, 1991). While the effects of anesthesia on P2 were not described in these studies, it is apparent in their figures that P2, like N1, was abolished. This contrasts with the effects of natural sleep where P2 is either unchanged or becomes larger. Recently, Van Hooff, De Beer, Brunia, Cluitmans, Korsten, Tavilla, and Grouls (1995) examined the effects of propofol/alfentanil anesthesia on N1-P2 waveforms. Their results closely resembled those seen in natural sleep, in that there was a marked decrease of N1 and an enhancement of P2. P2 was also delayed with anesthesia and, as such, was labelled by the authors as "P375". It is possible therefore that the differential effects on P2 may be due to different anesthetic agents employed in these studies.

Relatively few studies have examined AEPs in REM sleep. In REM sleep, N1 and P2 begin to resemble the waking waveforms. Weitzman and Kremen (1965) found a re-emergence of N1 and a P2 which was similar in amplitude to that seen in wakefulness. Campbell et al. (1992) and Campbell et al. (1988) reported that the amplitudes of N1 and P2 may return to approximately 50% of their waking amplitudes.

A dramatic effect of sleep on the AEP is the appearance of a large negative wave at approximately 350 ms, and thus labelled "N350". It has also been referred to as the "sleep N2" (Näätänen & Picton, 1987) to distinguish it from the N2 observed in the waking AEP. This late N2 or N350 may be observable in the unaveraged raw EEG as the "vertex sharp

wave" (Campbell et al., 1992). During the sleep onset period, this sleep N2 begins to emerge in Stage 1 sleep (Ogilvie et al., 1991; Harsh et al., 1994). This negativity may represent a manifestation of the waking N2 complex of waves that has a longer latency and an enhanced amplitude in sleep. On the other hand, it may represent a response that is unique to sleep. Studies involving the presentation of single tone repetitions have reported that N350 amplitude increases in NREM sleep, but is close to waking levels in REM sleep (Williams et al., 1964; Weitzman & Kremen, 1965; Williams, Hammack, Daly, Dement, & Lubin, 1965; Kevanishvili & von Specht, 1979; Ujszaszi & Halàsz, 1986; Ujszaszi & Halàsz, 1988; Campbell et al., 1992). Fruhstorfer & Bergstrom (1969) found the opposite effect of a decreased N350 latency in sleep relative to wakefulness. Ornitz, Ritvo, Carr, La Franchi, and Walter (1967) noted that the sleep N2 showed its greatest amplitude in the first ten minutes following sleep onset and then decreased and stabilized as the night progressed.

Recent studies have employed "oddball" stimulus conditions to examine the sleeping subject's ability to discriminate stimuli (Paavilainen et al., 1987; Nielsen-Bohlman, 1991; Campbell et al., 1992; Salisbury, Squires, Ibel, & Maloney, 1992; Salisbury & Squires, 1993; Harsh et al., 1994; Winter, Kok, Kenemans, & Elton, 1995). The oddball paradigm involves the presentation of infrequent deviant tones interspersed among a background of frequent standard tones. Subjects may be instructed to count the deviants or ignore all the stimulus presentations. Nielsen-Bohlman et al. (1991) used a large frequency separation (1000 vs 1500 Hz) and slow presentation rate (ISI=1 s) and observed a negativity following the deviant stimulus in NREM sleep at approximately 340 ms. Similar findings were obtained by Winter et al. (1995) who observed a negative peak in NREM sleep at

approximately 330 ms. Salisbury et al. (1992) also used a widely deviant (frequency/intensity) stimulus condition but reported no amplitude or latency differences between the N2 recorded in a waking reading condition and Stage 2 sleep. Harsh et al. (1994) had subjects attend (by making a behavioural response) or ignore deviant stimuli during the transition from wakefulness to sleep. They reported the emergence of a P220-N350-P450 complex at the onset of NREM sleep. The appearance of these waves corresponded to a decline in behavioural response latency. The amplitudes of these waves were greater across arousal states when the deviants were designated as targets than when they were ignored. Their N350 appears to be similar to that reported by Nielsen-Bohlman et al. (1991) and Winter et al. (1995).

In wakefulness, the presentation of oddball deviant stimuli may elicit a series of late positive components associated with P3. As discussed earlier, in waking selective attention tasks, a late P3 wave is elicited by attended and detected target deviants. The P3 is not elicited by the same stimulus in an unattended channel when it is ignored, suggesting that it is a strongly endogenous process. Evidence for the existence of P3 in sleep is equivocal. Given the strong association between attention and P3 elicitation in waking subjects it might be expected that the P3 would be strongly attenuated, if not abolished, in sleep. A number of authors have reported that the P3 is not present in sleep (Paavilainen et al., 1987; Kutas, 1990; Campbell et al., 1992). Others have presented data suggesting that a late P3 positivity may persist shortly after sleep onset (Wesensten & Badia, 1988; Bastuji, Garcia-Larrea, Franc, & Mauguière, 1990; Harsh, Voss, Hull, & Williamson, 1990; Hull, Harsh, & Badia, 1990; Nielsen-Bohlman et al., 1991). Bastuji et al. (1990) observed a late positivity at 450

ms in REM but not in non-REM sleep. Salisbury et al. (1992) reported that a small amplitude positivity in the P3 latency range was elicited by tones with large frequency/intensity deviations during non-REM Stage 2 sleep. In the paradigm used by Harsh et al. (1994), a P3 occurred when subjects made behavioural responses during waking and the latency of P3 increased with increasing response latency. P3 was absent when responding ceased. During sleep, a late positivity was evident at approximately 450 ms in early Stage 2 (5 minutes after initial Stage 1). There is considerable debate whether the late positivities peaking between 450 and 800 during sleep are, in fact, delayed P3s. For example, Nielsen-Bohlman et al. (1991) observed a late positivity in NREM that had a more central scalp distribution than the more parietally distributed waking P3. It may have thus reflected a P3a component.. Squires et al. (1975) reported the P3a to have a more anterior distribution than the P3. Another possibility is that this wave represents the positive deflection seen to follow the N350 or the K-Complex (see below). During isoflurane anesthesia (Plourde & Picton, 1991), P3b was found to be attenuated. A small amplitude P3a was however observed during sufentanil anesthesia (Plourde et al., 1993). In patients infused with propofol/alfentanil anesthesia, Van Hooff et al. (1995) also reported the presence of a small P3a to deviant stimuli.

Deviant stimuli presented in sleep will also elicit a late complex of large amplitude waves consisting of a negative peak at approximately 550 ms (N550) and a positive peak at approximately 900 ms (P900). This response has been termed the evoked 'K-Complex' (Halàsz, Pal, & Rajna, 1985; Ujszaszi & Halàsz, 1986; Bastien & Campbell, 1992). K-Complexes may also occur 'spontaneously' and are observable in the raw EEG during

NREM sleep stages 2, 3 and 4. Neither evoked nor spontaneous K-Complexes occur in wakefulness or REM sleep. The K-Complex is most likely to be elicited by stimuli that are loud, abrupt and that occur infrequently (Campbell, Bell, & Deacon-Elliott, 1985; Bastien & Campbell, 1992; Bastien & Campbell, 1994). A number of studies have shown that the N350 often precedes the K-Complex. In fact, it has been argued by some (Ujszaszi & Halàsz, 1986) that the N350 is a part of the K-Complex. Bastien and Campbell (1992) compared trials during which a K-Complex was or was not elicited. When a K-Complex was elicited, a preceding N350 was always present. Trials without K-Complexes were associated with low amplitude N350s. These authors hypothesized that once the N350 reached a certain threshold amplitude that it triggered the N550-P900 complex. It has been demonstrated however that the N350 and N550-P900 show differential scalp distributions, indicating they are separate cerebral events (Ujszaszi & Halàsz, 1986). Salisbury and Squires (1993) recorded ERPs to frequency and intensity oddball stimuli. They noted that the deviants elicited N2-P3 components in Stages 2 and 4 that could be dissociated from the longer latency N3 and P4 components of the evoked K-Complex. They concluded that two complexes of waves were distinct events, the latter being sleep-specific.

The Mismatch Negativity

In awake and alert subjects, an infrequent, physically deviant stimulus presented among a series of frequent homogenous stimuli, will elicit a negative "N2" wave in the AEP, peaking at approximately 200 ms. The N2 has been hypothesized to reflect a cerebral stimulus deviance detection process (Snyder & Hillyard, 1976; Näätänen et al., 1978). It is

not known whether the waking N2 is identical to that recorded in sleep. The waking N2 is elicited by deviant stimuli regardless of their task relevance (Näätänen et al., 1978; Näätänen et al., 1982). Näätänen et al. (1982) demonstrated that N2 is comprised of at least two subcomponents. The first, labelled the N2a, represented the automatically (i.e., independent of attention) elicited "mismatch negativity" (MMN) first described by Näätänen et al. (1978). The second component, termed the N2b, had a slightly longer latency and appeared as a 'sharper' negative peak superimposed on the descending portion of the N2a. The N2b was elicited only by widely different deviants that were actively attended by the subject. The N2b also had a less anterior scalp distribution than the N2a. The authors concluded therefore that the two processes represented distinct cerebral events. The N2 thus consisted of an exogenous mismatch component (N2a or MMN) and an attention-dependent endogenous component (N2b).

There is considerable evidence suggesting that the MMN is specific to the auditory modality (Nyman, Alho, Laurinen, Paavilainen, Radil, Reinikainen, Sams, & Näätänen, 1990; review by Näätänen, 1992). An N2 can be elicited in visual discrimination tasks (Ritter, Simson, & Vaughan, 1983) but evidence concerning its relationship to the MMN seen in audition is unclear. A visual MMN, analogous to the auditory MMN, has not been reliably recorded (Näätänen, 1992). The MMN is elicited by a variety of auditory stimulus changes including frequency (Näätänen et al., 1978; Sams, Paavilainen et al., 1985; Paavilainen et al., 1991; Novak, Ritter, & Vaughan, 1992a; Alho, Woods, & Algazi, 1994; Trejo, Ryan-Jones, & Kramer, 1995), intensity (Näätänen et al., 1987a; Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989; Näätänen, Paavilainen, Alho, Reinikainen, &

Sams, 1989; Winkler, Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1990; Woldorff, Hackley, & Hillyard, 1991; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993), and duration (Näätänen, Paavilainen, & Reinikainen, 1989; Paavilainen et al., 1991; Novak et al., 1992a; Novak, Ritter, & Vaughan, 1992b). A MMN can also be elicited by variations in inter-stimulus interval (Ford & Hillyard, 1981; Mantysalo & Näätänen, 1987; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987b; Nordby, Roth, & Pfefferbaum, 1988a; Nordby, Roth, & Pfefferbaum, 1988b; Böttcher-Gandor & Ullsperger, 1992), complex tones (Schröger, Näätänen, & Paavilainen, 1992; Schröger, 1994), phonetic structure (Aaltonen, Niemi, Nyrke, & Tuhkanen, 1987; Sams, Aulanko, Aaltonen, & Näätänen, 1990), spatial locus (Paavilainen, Karlsson, Reinikainen, & Näätänen, 1989; Schröger, 1995), and by stimulus omissions (Nordby, Hammerborg, Roth, & Hugdahl, 1994). Recently, Schröger (1995) reported that stimuli deviating in two dimensions (pitch and spatial location) elicited larger amplitude MMNs than stimuli deviating in either pitch or spatial location alone.

Näätänen and colleagues have hypothesized that the MMN reflects a type of sensory memory comparison process (Näätänen, Paavilainen, Alho et al., 1989). According to this theory, the physical attributes of the standard stimulus are maintained in short term sensory memory in the form of a neuronal trace. When a deviant stimulus is presented, its physical features are compared to the memory trace established for the standards. If a mismatch is detected, the MMN is elicited. An alternative view holds that the MMN is produced by the activation of 'fresh neural elements' by the deviant stimulus (see Näätänen, 1992). In the typical oddball paradigm, standard stimuli are presented more frequently than are deviants. It is thus possible that neuronal fields may become more refractory for the standards than for

the deviants resulting in a greater response to the deviant stimuli. Another possibility is that there are neurons which differentially respond to particular stimulus features. In the auditory modality there may be neurons that are specific to certain stimulus frequencies or intensities, and these become freshly activated by pitch-deviant or intensity-deviant tones.

There is converging evidence to support the memory trace theory of MMN generation. The MMN is not elicited by the first stimulus in a sequence (Näätänen, Paavilainen, Alho et al., 1989). This suggests that, unlike the N1 response, the MMN is not the result of a change from "no input" to "input" or vice versa. Rather, two different, yet temporally proximate inputs are required. It has also been shown that the MMN can be elicited by the omission of a stimulus in a sequence (Nordby et al., 1994). This situation differs from the previous example because in this case a memory trace is formed for the frequent stimulus. Upon its omission, a change is detected an the MMN is elicited. This finding is also not easily explainable by the activation of fresh neural elements.

The MMN is influenced by the rate of stimulus presentation. The MMN is largest to stimuli that are presented quite rapidly (i.e., every 100 to 600 ms). Stimuli presented rapidly, especially large deviants, may elicit a MMN that shows temporal overlap with the N1 thereby enhancing the amplitude of that component (Näätänen et al., 1982). However, standards presented rapidly without intervening deviants, will reduce the amplitude of N1.

Mantysalo and Näätänen (1987) found that an MMN was elicited by stimulus sequences with constant inter-stimulus intervals (ISIs) of 1 or 2 seconds, but not 4 or 8 seconds. Sensory memory fades rapidly. The fact that the MMN rapidly decreases in amplitude with an increase in the inter-stimulus interval is consistent with this. The sensory

memory for the standard stimulus will fade before the onset of the deviant. If there is no standard available for comparison, the MMN will not be elicited. The sensory memory trace may remain active as long as ten seconds (Böttcher-Gandor and Ullsperger, 1992; Sams, Hari, Rif, & Knuutila, 1993).

Additional evidence suggests that more than one trace can be maintained in sensory memory at one time. Winkler, Paavilainen, and Näätänen (1992) recorded MMNs to stimulus sequences in which features of the standard stimulus was varied within a block of trials. Thus the deviants were being "compared" to multiple standards. When they examined local stimulus sequences within the blocks they found that the MMN was still elicited by deviants preceded by sequences of mixed standards. This was interpreted as evidence that a more than one stimulus trace could be maintained in the memory store.

In general, it appears that MMN amplitude increases and its latency decreases with increasing magnitude of stimulus deviance. This was demonstrated for frequency deviations by Sams, Paavilainen et al. (1985) who found the MMN became larger and shorter as the pitch separation between the deviant and standard tones was increased. The MMN can be dissociated from the N1 by decreasing the magnitude of stimulus deviance. In such instances, the MMN may peak considerably later than the N1. The amplitude of the MMN seems to plateau however at higher levels of deviance (Novak et al., 1990; Sams Paavilainen et al., 1985), at least for frequency changes. No saturation in MMN amplitude was observed by Näätänen, Paavilainen, Alho et al. (1989) for increasingly large decrements in stimulus intensity. Paavilainen et al. (1989) found increasing MMN amplitudes for increasing deviations in interaural spatial location of a stimulus. Perhaps the magnitudes of deviance

used in these studies were not sufficient to attain a plateau effect.

As the probability of deviant stimulus occurrence within a sequence decreases, the amplitude of the MMN increases. Näätänen (1992) reported data showing that a deviant with a 2% probability of occurrence elicited a greater MMN response than a deviant with a 10% probability of occurrence. On the other hand, Sams, Alho, and Näätänen (1983) found that a MMN could be elicited by a sequence consisting of two equiprobable stimuli. When local stimulus probabilities were examined within the sequence it was noticed that the MMN was elicited when one stimulus was preceded by more than one "exemplar" of the other stimulus. Furthermore, as the number of immediately preceding exemplars increased, the magnitude of the MMN also increased. Scherg, Vajsar, and Picton (1989) found that the predictability of the deviants within the sequence had no effect on the MMN. Thus the critical factor remained probability of occurrence and not predictability.

The MMN is maximal at fronto-central areas of the scalp. Näätänen & Michie (1979) postulated the existence of two subcomponents of the MMN, one generated in the supratemporal plane of the auditory cortex and the other in frontal cortex. They proposed that an early temporal component reflected a sensory-specific mechanism involving the preconscious detection of stimulus deviation. This in turn activated the later frontal component which led to the conscious discrimination of stimulus deviance. The existence of two MMN subcomponents was confirmed by Giard, Perrin, Pernier, and Bouchet (1990) who applied current source density analysis to ERPs recorded during a selective attention task involving tones slightly deviating in pitch. Their results revealed two bilaterally represented subcomponents to the frequency MMN that differed in latency and scalp distribution. The

first component was an early sensory-specific, contralaterally larger wave believed to be generated around the auditory cortex. The second component was a later, non-specific frontal wave that was larger over the right hemisphere regardless of the ear of stimulation. Previously, Scherg et al. (1989), using their dipole source analysis, also reported the presence of two generator sources for the supratemporal MMN. They however did not find evidence of a frontal source. Paavilainen et al. (1991) explained that this might have been due to the use of fewer frontal electrodes by Scherg et al. (1989) compared to Giard et al. (1990), and the "pooling" of data from both hemispheres.

There is further evidence supporting the existence of a temporal generator source for the MMN. When a nose reference electrode is used, the MMN will invert in polarity below the Sylvian fissure, resulting in a positive-going deflection at the mastoid recording site (Alho, Paavilainen, Reinikainen, Sams, & Näätänen, 1986). The positive deflection of the MMN at the mastoid suggests that the dipole source of the MMN may be located in temporal auditory cortex. Polarity reversal at the mastoid has been used to distinguish the MMN from other negativities such as the N2b (Sams, Paavilainen et al., 1985; Giard et al., 1990). The N2b does not invert at the mastoid (see Näätänen et al., 1993) . Sams and colleagues (Sams, Hämäläinen, Antvero, Kaukoranta, Reinikainen, & Näätänen, 1985; Sams, Kaukoranta, Hämäläinen, & Näätänen, 1991) reported magnetoencephalographic (MEG) evidence suggesting the presence of an MMN source in the supratemporal auditory cortex. Kropotov, Näätänen, Sevostianov, Alho, Reinikainen, and Kropotova (1995) recently reported that an intracranially recorded MMN could be detected in a small area of primary auditory cortex.

There are data available concerning the scalp distributions of MMNs to different types

of stimulus change. Paavilainen et al. (1991) recorded the MMN to stimuli deviating in frequency (650 Hz), duration (20 ms), and intensity (70 dB). In separate conditions, these deviants (p=.10) were presented with 600 Hz, 50 ms, 80 dB standards. All three stimulus conditions elicited a MMN. There was a right hemispheric dominance for each MMN regardless of the ear of stimulation. This interhemispheric difference was smallest however for the frequency MMN. In addition, all three types of MMNs inverted in polarity at the mastoid. The frequency and duration MMNs appeared to be comprised of two sequential negative components. The first negativity inverted in polarity at the mastoid, but the second did not. The authors suggested that the early negativity may have been comprised of the two supratemporal subcomponents reported by Giard et al. (1990) and the latter negativity represented Giard et al.'s late frontal component. Sams, Hämäläinen et al. (1985) also recorded MMNs, in separate conditions, to stimuli deviating in frequency (1500 Hz), intensity (67 dB), and duration (50 ms). Standard stimuli were 1000 Hz, 90 dB, 100 ms tones. Their MEG recordings indicated that the mean locations for the equivalent dipoles for the three types of MMNs did not significantly differ from each other. In addition, these MMN fields were more anterior than those to their respective N100 counter-parts.

Näätänen (Näätänen, 1991; Näätänen et al., 1993; Näätänen & Alho, 1995) has proposed that the supratemporal component of the MMN is generated by two types of neuronal fields. The first, referred to as *computational* or *informational* neurons, are responsible for the elicitation of the MMN. The second type are *amplifying* or *modulating* neurons which determine the magnitude of the response. Whereas the computational component reflects the detection of the mismatch, the activity of the amplifying neurons

account for variations in MMN amplitude related to the physical features of the stimulus deviance (extent of frequency, amplitude mismatch, etc.) and vigilance states (attention, drug effects, etc.). The activity of these two overlapping processes may correspond to the early sensory-specific component of the MMN first proposed by Näätänen and Michie (1979) and later confirmed by the recordings of Giard et al. (1990). When the supratemporal component reaches a certain threshold, as determined by the activation of the amplifying system, the second frontal MMN component may be triggered. Paavilainen et al. (1991) postulated that this frontal component may thus constitute a link between the sensory-specific cortex and the activation of N2b and P3a generator processes.

(i) Frequency Deviance

The auditory deviance manipulation most often employed for the elicitation of the MMN has involved changes in tonal frequency (or pitch). In the first study describing the MMN, Näätänen et al. (1978) recorded ERPs to 1140 Hz deviant and 1000 Hz standard tones, and observed a 'negative shift' at approximately 150 ms for the deviants. The ERP following the deviant was overlapped by a relatively long latency negative wave that peaked at approximately 150 ms. This negativity was termed the mismatch negativity (MMN).

Sams, Paavilainen et al. (1985) systematically explored the effects of different magnitudes of frequency deviation on the MMN. They presented different blocks of stimuli with deviants (p=.20) of 1002 Hz, 1004, Hz, 1008 Hz, 1016 Hz, or 1032 Hz presented among 1000 Hz standards (p=.80). No MMN was apparent for the 1002 or 1004 Hz deviants. At 1008 Hz a small amplitude MMN was observed. Larger MMNs of equal

amplitude were evident for the 1016 and 1032 Hz deviants. In addition, the peak latency of the MMN decreased with increasing level of deviance. The amplitude data indicated that the MMN increased for increasing frequency deviance and that it saturated at higher magnitudes of deviance. There appeared however to be a minimum 'threshold' of change necessary for the elicitation of the MMN because no change was seen for the deviants below 1008 Hz. In a separate deviant discrimination condition, they found that the 1008 Hz level also corresponded to the threshold for the subject's perception of the frequency change. That is, at the 1008 Hz level, the subjects had difficulty perceiving the difference between the deviant and standard tone pips and no MMN was apparent. This suggested a relationship between the MMN and the perception of frequency change.

Näätänen and Gaillard (1983) reported data indicating the presence of a MMN in the absence of subjective pitch discrimination. Standard tones of 1000 Hz were presented with deviants near the discrimination threshold (this was determined for each subject based on his or her discrimination accuracy and approximated 1010 Hz). The subject was instructed to respond if they detected the target deviant. A different response was made when they were uncertain if the deviant had been presented. The ERPs were then divided into detected, non-detected and "not sure" categories. They found that a MMN was elicited by the non-detected deviants and that it was similar in amplitude to the detected and "not sure" responses. A late positivity was elicited only by the detected and "not sure" deviants. These findings suggest that the MMN is an automatic response that may be elicited *even in the absence of conscious perception of stimulus deviance*. According to Näätänen (1992), the MMN may be necessary but not sufficient for the conscious perception of stimulus change. In the data of Sams,

Paavilainen et al. (1985), discussed above, the MMN may have been elicited in the absence of perceptual discrimination, but at such low magnitudes of deviance, the signal-to-noise ratio may not be sufficient to observe the response. In another discrimination study, Novak et al. (1990) noted that MMNs to detected pitch deviants were time-locked to the elicitation of subsequent N2b-P3a components. This is further support for the MMN playing a role in stimulus discrimination.

Early studies indicated that the frequency MMN was independent of the subject's level of attention (see review by Näätänen, 1992). Sams, Paavilainen et al. (1985) presented pitch-deviant tone sequences during an attend and an ignore condition. They found no differences between the MMN to the attended and ignored deviants. In the attend condition, detection of the infrequent, deviant stimulus elicited a N2b-P3 complex in addition to the MMN. The ignore condition used by Sams, Paavilainen et al. (1985) required subjects to read a book. Most studies now typically record the MMN while subjects attention is directed away from the auditory stimuli. This circumvents the problem of an overlap by the N2b-P3 components when subjects are asked to detect the deviant stimulus.

The rationale for the use of the of an ignore paradigm is based on the assumption that the MMN is not affected by attention. This assumption is now being questioned based on the findings of recent studies. Alho, Woods, Algazi, and Näätänen (1992) and Woods, Alho and Algazi (1992) conducted studies on intermodal selective attention involving deviant auditory and visual stimuli. They found that to-be-ignored auditory frequency deviants elicited MMNs that were attenuated in amplitude relative to target deviants. This effect was only noted for small frequency changes, and not for large deviations. Alho (1992) postulated

that attention may only modulate the MMN for those changes that are small or close to the discrimination threshold. One problem with these studies was that the subject was instructed to respond to the attended deviants. Thus the difference in amplitudes between the attended and ignored deviants may have been attributed to the superimposition of target-related negativities such as the N2b or movement-related cortical potentials associated with the motor response.

In a later study by Alho et al. (1994), the superimposition of target-related negativities onto the MMN was controlled by presenting rare target (requiring a behavioural response) and non-target (not requiring a response) to-be-attended deviants. Once again, auditory and visual selective-attention tasks were used. Stimuli consisted of 1000 Hz standard tones presented with either 1050 Hz or 1300 Hz deviant tones delivered randomly to the left and right ears at random ISIs between 200 and 400 ms. The probability was 37.5% for the standards and 5% for each of the deviants, per ear. The remaining 5%of the stimuli were visual presentations occurring at mean intervals of 6 seconds. During auditory attention, subjects attended to the designated ear and responded only to the 1300 Hz deviants, thus apparently ignoring the 1050 Hz deviants.[3] During visual attention, subjects responded to the visual stimuli and ignored all the tones. MMNs were elicited by both the 1050 Hz and 1300 Hz deviants regardless of whether they occurred among attended or unattended tones. In contrast to the previous findings of Alho et al. (1992) and Woods et al. (1992), the amplitudes of the MMNs to the attended and unattended small frequency deviants were not

[3] In order to not respond to the non-target deviant, the subject would have to compare it to a memory trace for both the standard and the target deviant. This would presumably require some form of processing. Thus, even non-targets would probably elicit an N2b wave.

different. The authors concluded that when the attended deviant is not designated as a target to be detected, the MMN elicited is not attenuated relative to that elicited by the same deviant in an unattended channel. Thus the frequency MMN, even for small separations, is not influenced by attention.

Näätänen et al. (1993) also recorded ERPs to target and non-target deviants in a selective-attention paradigm requiring a strong attentional focus. Two types of deviant stimuli were used which differed from standards in frequency. Subjects were presented with 475 Hz deviants and 500 Hz standards to the left ear and 1050 Hz deviants and 1000 Hz standards to the right ear. These tones were all presented at 80 dB. (Intensity deviants were also presented at 70 dB, but these results are discussed in a later section). The probability was .46 for the two standards and .02 for each of the four deviants (a frequency and an intensity deviant to each ear). Stimuli were presented quite rapidly, the ISI varying between 70 and 200 ms. In four different conditions, subjects were instructed to count either the frequency or intensity deviants in either the left or right ear. A reading condition was also employed in which the subjects were instructed to ignore all tone presentations to both ears. This procedure allowed for the examination of the ERPs for each deviant as it related to the target stimulus in the following conditions: (1) attend, the deviant itself as target (correct ear, correct attribute); attend, different-attribute deviant as target (correct ear, wrong attribute); non-attend, same-attribute deviant as target (wrong ear, correct attribute); non-attend, wrong-attribute deviant as target (wrong ear, wrong attribute); and no auditory stimulus as target (reading). The results indicated no "target effect" on the frequency MMNs since the MMN negativities were the same for the "correct ear, correct attribute" and the "correct ear, wrong

attribute" ERPs. In addition, there was no "attention effect", as indicated by polarity-reversed MMNs at the mastoid and occipital locations, because the amplitudes of the MMNs in the "correct ear, correct attribute" were similar to those in the "reading condition". The authors cautioned however that the amplitudes of these MMNs were quite small and thus the statistical tests of significance may not have been powerful enough to show deviation from the null hypothesis.

In a recent study, Trejo et al. (1995) recorded MMNs to a binaurally presented stimulus composition consisting of 1200 Hz standard tones (p=.80) interspersed among 1000 Hz (p=.10) and 1400 Hz (p=.10) deviants. The tones were presented at a mean ISI of 310 ms (range 210-410 ms) and superimposed on a background narrative. In one task, subjects were instructed to respond to a specified deviant tone by pressing a button, thus ignoring the other deviant tone, the standard and the narrative. In a second task, subjects were instructed to respond to the target word "and" in the narrative and ignore all the tones. The resulting difference waves for both the target and non-target deviants could be divided into two distinguishable negative peaks occurring in the MMN latency range at approximately 100-180 ms and 200-300 ms. Both peaks were larger for the target than for the non-target deviants. The second peak was deemed to be largely attributable to the N2b. The earlier peak was however interpreted to represent an attentional enhancement of the MMN. This contrasted with the earlier findings of Näätänen et al. (1993) by suggesting that the frequency MMN was susceptible to attentional influences.

There are several problems with the study by Trejo et al. (1995). First, they recorded their ERP data from electrode sites Fz, Cz, Pz and the right mastoid, all referenced

to the left mastoid. This montage does not adequately allow for the observation of polarity reversal across the Sylvian fissure indicative of the MMN (the use of a nose reference is recommended, see Alho et al., 1986). The data from the right mastoid were not reported. Consequently, it was difficult to dissociate the effects of N2b overlap from the MMN. The N2b is also large over the midline but does not invert at the mastoid (Sams et al., 1985). Second, the use of the button press allowed for possible contamination of the ERP by motor potentials associated with performing the response. Third, since all stimuli presented were "attended", the early negative peak may have been influenced by enhancement of the N1 in the form of processing negativity which is larger for deviants than for standards (Näätänen & Michie, 1979).

The findings concerning attentional and the frequency MMN indicate that it is highly resilient to attentional modulation. Attentional effects that have been observed for large frequency deviants may be confounded by other overlapping processes. An attenuation of the MMN may be observed however for small frequency deviants when the subject is strongly forced to direct attention toward another stimulus input.

(ii) Duration Deviance

Näätänen, Paavilainen, and Reinikainen (1989) demonstrated that a MMN could be elicited by stimuli deviating in duration. In a series of deviant-decrement conditions, they presented infrequent deviant tones that were one-half the duration of frequent standards. These included: 25 vs 12.5 ms, 100 vs 50 ms, 200 vs 100 ms, and 400 vs 200 ms. Two deviant-increment conditions were also used where the deviant s were twice the duration of

the standards: 25 vs 50 ms, and 100 vs 200 ms. A MMN was evoked by the deviant stimuli in all conditions. The peak latency of the MMNs varied across conditions. The occurrence of the MMN was contingent upon the temporal relationship between the standard and deviant tones. In the decrement deviant conditions, the latency of the MMNs gradually shifted earlier in time as the difference in the duration of the tone pairs (standards and deviants) decreased. Similarly, in the increment deviant conditions, the latency of the MMN became earlier as the difference in the duration of the tone pairs decreased.

The inclusion of both a deviant increment and decrement condition demonstrated that the MMN was dependent upon the comparative relationship between the deviant and the standard, and not upon the deviant stimulus alone. For example, the 50 ms deviant elicited a later MMN peak when it was presented in conjunction with the 100 ms standard than when it was presented with the 25 ms standard. This is because, in the former case, it took at least 50 ms before the response to the deviant could be initiated. In the latter case, the deviant could be recognized after only 25 ms. The duration deviance manipulation provides a useful means of temporally dissociating the MMN response from other ERP components related to the processing of stimulus deviance. Other AEP components which are responsive only to the deviant should show no temporal displacement between these two conditions.

The use of increments in the duration of deviant stimuli may cause a possible confound. Long duration stimuli will elicit a slow negative wave, the sustained potential (Picton, Woods, & Proulx, 1978). The duration of the sustained negative potential is dependent upon the duration of the stimulus. If the duration of the deviant is longer than that of the standard stimulus, the sustained negativity will last longer for the deviant. Thus, a

difference in negativity following the deviant could be due to the mismatch process or the sustained potential. It is unlikely that a negativity will be sustained for stimuli whose duration is as brief as those employed in the typical MMN study. Nevertheless, in order to dissociate sustained and MMN processes, Näätänen, Paavilainen and Reinikainen (1989) included a condition in which brief deviants (duration not specified) were presented alone without the intervening longer duration standards. The time between the deviants was the same as in the standard-deviant condition. If the increased negativity were due to the sustained potential, it should have still been present in this condition. If the negativity were due to the MMN, it would not be present in this condition since there were no standards to compare to the deviants. The increased negativity was not observed. It was concluded therefore that the increment deviant also elicits a MMN.

The MMN to duration deviant stimuli has been studied in awake subjects by a number of other researchers (Näätänen, Paavilainen, & Reinikainen, 1989; Paavilainen et al., 1991; Novak et al., 1992a; Novak et al., 1992b). Paavilainen et al. (1991) recorded the MMN using duration deviant decrements of 20 ms presented among a background of 50 ms standards. Stimuli were presented to both the left and right ears of subjects. They reported the MMN to be larger over the right hemisphere, regardless of ear of stimulation. Sams et al. (1991) reported the elicitation of an neuromagnetic equivalent of the duration decrement MMN using 100 ms standard tones and very infrequent (3.3%) 50 ms deviants. Novak et al. (1992a) used a duration deviance condition involving 100 ms frequent and 170 ms rare tones. Subjects were required to discriminate between the stimuli by making a finger-lift response to the target 170 ms tones. The deviants elicited a MMN in addition to target-related N2b and

P3 responses (Loveless, 1986). In a second study, Novak et al. (1992b) attempted to control for the effects of N2b overlap. They utilized the same stimulus duration manipulation with the additional requirement that subjects only respond to longer duration targets of a designated pitch. They found that the long duration deviants elicited MMNs of similar amplitude regardless of whether they were targets or non-targets.

The findings obtained thus far for the MMN to duration changes indicate that, like the frequency MMN, it is largely unaffected by attentional factors. These studies did not however employ stimulus or task conditions that are optimal for the establishment of a strong attentional focus away from the eliciting stimulus. Thus the attenuating effect of highly focused attention demonstrated for the frequency MMN has not been adequately investigated for duration changes.

(iii) Intensity Deviance

In the original study by Näätänen et. al. (1978), a MMN to increases in stimulus intensity was recorded. This work supported a previous report by Snyder and Hillyard (1976) of an enhanced N2 to deviant intensity increments. In the earlier data however, the MMN or N2a could not be separated from the N2b. Näätänen et. al. (1987a) recorded ERPs to both increments and decrements in stimulus intensity during an ignore (reading) condition. In separate blocks, 84 dB increment and 74 dB decrement deviants were presented with 80 dB standards.[4] They found a MMN was elicited by deviants in both conditions but was

[4] The magnitude of physical difference between the deviant and standard stimuli used by Näätänen et al. (1987a) were not equivalent in the increment and decrement conditions. The increment deviants differed from the standards by 4 dB whereas the decrements differed from the standards by 6 dB. A wider separation for decrements may have been used to control for possible "perceptual" differences

larger in amplitude for the intensity decrements. The authors reasoned that a larger response in the MMN latency range for the increments, relative to the standards, could have been partially attributable to an enhancement of the N1, since N1 amplitude increases with increasing stimulus intensity (Näätänen & Picton, 1987). N1 enhancement could not however account for the increased negativity to the decrements. Näätänen, Paavilainen, Alho et. al. (1989) recorded ERPs to a series of graded intensity decrement stimulus conditions (57 dB, 70 dB, or 77 dB deviants; 80 dB standard). The MMN was elicited in each condition and the amplitudes were found to be larger with increasing magnitude of deviance. This finding demonstrated that the negativity was due to the MMN and not an enhanced N1. If N1 enhancement was responsible for the increased negativity, then the 77 dB deviant should have elicited a larger response than the 57 dB deviant. The results showed the reverse to be true.

Alho et al. (1989) recorded MMNs to intensity decrements in a complex dichotic listening task. They presented 60 dB deviant tones (p=.20) among a background of 75 dB standards tones (p=.80) at an inter-stimulus interval of 410 ms. In different conditions, the location of the tones (left vs right ear) was either held constant or varied and the pitch (1000 Hz vs 3000 Hz) was either held constant or varied. Subjects were instructed to count the infrequent low intensity deviant either in a designated ear (irrespective of pitch) or at a designated pitch (irrespective of ear). They found the MMNs elicited by the intensity

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related to stimulus intensity change. Subjects may perceive a change involving a louder stimulus to be greater than a change involving a softer stimulus, even if the actual physical differences are the similar. Also, a 6 dB decrease and a 4 dB increase in intensity will produce a similar change in the power (or energy) of the auditory stimulus.

deviants were not significantly different between the attend and ignore conditions. Thus the intensity MMN was the same regardless of whether the deviant occurred in an attended channel or unattended channel. These findings were consistent with those discussed previously for frequency and duration changes.

Woldorff et al. (1991) conducted a similar selective attention study on the intensity MMN, but the tasks were designed to establish a stronger attentional focus for subjects. A small intensity decrement discrimination was used (35-45 dB deviant vs. 55 dB standard) and deviants occurred with very low probability ($p=.09$). Stimuli were very short duration (13 ms) and presented at very rapid rates (ISI = 120-320 ms). The aim was to make the task difficult in order to maximize the amount of attention directed toward the relevant stream of input and away from the irrelevant stream. In alternating fashion, subjects were instructed to attend to stimuli presented to one ear, and to detect the deviants, while ignoring stimuli presented to the other ear. Unlike most previous MMN studies, they found an enhanced negativity for attended deviants relative to physically identical unattended deviants. Thus, when subjects were forced to focus attention in order to carry out task requirements, the MMN to intensity deviants was reduced during inattention compared to attention conditions.

These findings conflicted with those of Alho et al. (1989) who employed similar tasks and observed no negative enhancement to attended deviants. Näätänen (1991) explained this discrepancy by stating that perhaps the 410 ms inter-stimulus interval used by Alho et al. (1989) was still too long (compared to the 120-320 ms ISI used by Woldorff et al., 1991) to observe the attention effect. In the task used by Alho et al. (1989), because the stimuli were presented relatively slowly, it might have been possible to switch attention to the to-be-

ignored channel. Rather than focusing on the designated input, subjects may have been dividing their attention between the to-be-attended and the to-be-ignored channels.

The findings of Woldorff et al. (1991) were subsequently confirmed in the study conducted by Näätänen et al. (1993; described earlier for frequency deviance). They presented slight inensity decrements (70 dB deviant; 80 dB standard) at rapid rates (70-200 ms) to subjects in a selective-listening paradigm. A reading condition was also used in which subjects were instructed to ignore all tones. In the selective-attention phase, they found that the deviants presented to the unattended channel elicited a lower amplitude MMN than the same deviants presented to the attended channel. This greater negativity for the attended deviants was attributed to an N2b overlap. The MMN to the intensity deviants in the reading condition however was also larger than the MMN to the unattended deviants in the selective-listening task. This suggested a genuine effect of MMN attenuation to unattended deviants during selective-listening.

The authors proposed that the larger MMN observed for attended deviants was not due to an enhancement of the attended-channel negativity, but to a comparative decline in the unattended-channel response owing to the absence of attentional resources. The results were interpreted as reflecting a genuine attenuation of the MMN to the unattended channel deviants, relative to the MMN obtained while subjects were reading. The larger MMN during the reading condition was not attributed to N2b influence because the N2b is usually not elicited in ignore conditions, especially when the magnitude of deviation is small. A small amplitude MMN was still apparent in the unattended channel. It is possible that this is a reflection of subject's inability to completely ignore deviants even under highly demanding

attentional conditions. In the majority of MMN studies, the "non-attend" condition typically employed is only to "read a book".

The MMN to intensity deviants may be more susceptible to attentional influences than other types of stimulus deviation. The MMN to unattended deviants may be attenuated relative to attended deviants. This effect seems most apparent under conditions involving highly focused attention.

The Mismatch Negativity in Sleep

The majority of data obtained from waking studies of the MMN indicate that, at least for frequency deviants, its elicitation remains independent of attentional influences. A notable exception appears to be the recent findings concerning the intensity MMN (Woldorff et al., 1991; Näätänen et al., 1993). The findings of Näätänen et al. (1993) did however indicate that the amplitude of the MMN can vary across different "ignore" conditions because of possible intrusions of the stimulus into the subject's awareness. It would appear that even with the most carefully controlled studies, it may be impossible for awake and alert subjects to completely ignore unattended stimuli. A possible means to resolve this dilemma is to record the MMN during sleep, the period of time in which subjects are least conscious of the external environment.

Csépe, Karmos, and Molnar (1987, 1988) were able to record an apparent MMN during sleep in freely moving cats using electrodes implanted in the auditory cortex. Tones, deviating in frequency (3000 vs. 4000 Hz), were presented at varying probabilities during wakefulness and slow wave sleep. They reported a MMN during both wakefulness and

sleep. The waking MMN occurred much earlier than that seen for humans, peaking at approximately 30-40 ms. The MMN in sleep occurred between 50-200 ms. Consistent with previous studies, the amplitude of the MMN was found to increase for decreasing deviant probability. Alho, Sainio, Sajaniemi, Reinikainen, and Näätänen (1990) reported a MMN to frequency changes in human newborns during "quiet sleep". They reported that 1200 Hz deviant tones presented among 1000 Hz standards elicited a greater N2 wave than did a series of 1200 Hz tones presented alone. This was interpreted as evidence of a MMN process. The negativity was the result of a stimulus comparison mechanism which was active at a very early age. Unfortunately, few methodological details were provided making verification difficult.

Paavilainen et al. (1987) were the first to attempt to record a MMN in sleeping human adults. They used a low probability ($p=.10$) pitch deviant oddball condition and presented stimuli at a fast rate. Their stimulus blocks (800 trials) consisted of infrequent 1050 Hz deviant tones interspersed among a train of 1000 Hz standard tones, presented at an inter-stimulus interval of 510 ms. The stimuli were presented to seven subjects during a waking ignore condition as they read quietly in bed prior to sleep. Subjects were then permitted to fall asleep and tones were presented during the next two hours of sleep. Sleep ERP data were obtained during "drowsiness" (waking EEG with alpha attenuation), Stage 1, Stage 2, and SWS (Stages 3 & 4 combined). No REM sleep data were acquired. In the reading condition, deviants tones elicited a fronto-central MMN in the 150-200 ms interval. In the drowsy state, a MMN was still evident in "some" of the subjects. The MMN was abolished however in Stage 1, and no significant differences between standard and deviant

waveforms were observed in any of the other sleep stages. In fact, no "sleep N2" was observed in any stage.

There are some problems with the study by Paavilainen et al. (1987). First, only a very slight frequency change was used. This small separation may not have been large enough to elicit a sleep-MMN. Second, only one block of trials was presented in each sleep condition. Thus the number of deviant responses obtained may not have been sufficient to obtain a clear MMN. The MMN rarely exceeds 1-2 μV in the waking state. During sleep, the signal-to-noise ratio may have been too small to observe the small amplitude MMN embedded in the large amplitude (exceeding 200 μV) background EEG characteristic of NREM.

Campbell et al. (1992) recorded ERPs to frequency deviant tones during an all-night sleep study. In a "large deviant" condition, 2000 Hz deviants (p=.40) were presented (ISI=2 s) with 1000 Hz standards (p=.60). A large number of trials were presented in wakefulness, during a reading condition and during SWS, REM, and Stage 2 sleep. Stage 2 was divided into "early" and "late" portions of the night. They reported a small amplitude MMN in wakefulness, as well as in Stage 2 (late) and REM sleep. The sleep-related MMNs had shorter latencies however than that seen in wakefulness. The amplitude of the MMN elicited in the reading condition was small given the large magnitude of deviance used. This may be due to two methodological shortcomings. First, the ISI employed was much longer than that used in most MMN studies. Second, the deviant probability was quite high, which also is not optimal for the elicitation of the MMN.

The findings of Campbell et al. (1992) suggest however that a MMN may be elicited

in sleep. The factors contributing to this response are uncertain however. The MMN was elicited only during sleep states occurring later in the sleep period. Stage 2 sleep, occurring later in the night, is characterized by a lower amplitude tonic EEG than Stage 2 early in sleep. Similarly, REM sleep, most of which occurs in the second half of the sleep period, is also characterized by a low amplitude EEG. These conditions may provide for a higher signal-to-noise ratio for the MMN to be observed.

Nielsen-Bohlman et al. (1991) presented deviant auditory stimuli to ten subjects during a waking ignore condition and a subsequent 40 minute nap. Sleep data were reported for Stage 2 and SWS. Deviant stimuli included both a 1500 Hz tone (p=.10) and a 300 ms complex 'novel' tone (p=.10) presented among 1000 Hz standards (p=.80). Tones were presented at a slow, constant ISI of 1 second. A MMN was elicited by both types of deviants in the waking condition. In sleep, a late negativity emerged at approximately 340 ms in response to the deviants. The authors were uncertain whether this negativity reflected the presence of a genuine MMN or the sleep-related N350 (perhaps part of the K-Complex). It is unlikely that the MMN, which usually occurs at approximately 100-300 ms, would be delayed this long. Moreover, the rate of stimulus presentation was again not optimal for the recording of the MMN.

Salisbury et al. (1992) presented two oddball conditions to seven subjects during waking (reading) and Stage 2 sleep. In one condition, 3000 Hz, 60 dB deviants (p=.01) were presented among 250 Hz, 40 dB standards (p=.09). Thus, deviant stimuli differed markedly from standards along two dimensions, frequency and intensity. In the second condition, the features of the deviant and standard stimuli were reversed. The ISI was 1.2 s

for both conditions. Only the data from the "louder"condition were reported. Their analyses revealed no significant latency or amplitude differences in N2 (highest peak occurring between 220-300 ms) recorded during wakefulness and Stage 2 sleep. They claimed that these preliminary findings were consistent with the view that the MMN is elicited automatically and therefore unaffected by sleep.

A recent study by Winter et al. (1995) also recorded ERPs from twelve subjects to oddball stimulus presentations in a waking ignore condition and Stage 2 sleep. Stimuli consisted of 2000 Hz large (p=.10) and 1200 Hz small deviant tones (p=.10) presented with 1000 Hz standards (p=.80) at an inter-stimulus interval of 1 second. In sleep, no negativity was evident in the waking MMN latency range. A late negativity was apparent in sleep for deviants, referred to as "N330", but it was much larger and occurred much later than the MMN seen in wakefulness. Furthermore, it did not show the same topographical representation as the waking MMN. The authors concluded therefore that it constituted a separate process, possibly an early component of the K-Complex.

Sallinen, Kaartinen, and Lyytinen (1994) recorded evoked responses from six sleeping subjects during the presentation of an oddball stimulus condition consisting of 1200 Hz deviant and 1000 Hz standard tones. Stimuli were presented with a very low deviant probability (p=.02), at an ISI of 625 ms. Tones were presented during a reading condition and during Stages 1, 2 , REM and SWS. No MMN was elicited in any stage of sleep. The data from Stage 2 were subsequently sorted into trials in which a K-Complex was either elicited or not elicited. They defined a K-Complex as being comprised of a N350-N550-P900 wave complex with a peak-to-peak amplitude of at least 75 μV. Analysis of these data

showed that a fronto-central negativity was evident in the MMN latency range on those trials where a K-Complex was present. When no K-Complex was elicited, no MMN-like negativity was observed. The putative sleep-MMN had a similar morphology to that seen in wakefulness, but with a slightly earlier (but non-significant) latency. It did not however show a polarity reversal at the mastoid site. These results provided evidence of a dissociation of the MMN from N350. Nevertheless, N350 and especially N550 are much larger in amplitude than the MMN. It is possible that N350 and N550 may overlap and summate to the earlier portion of the evoked potential waveform. Thus the small negativity that is recorded within the 100-300 ms latency range may be due to the temporal-spatial overlapping and summating effects of the later and much larger K-Complex. The authors suggested that the possible MMN may serve as a triggering mechanism for later processing in the form of the K-Complex.

The results of these studies indicate that the MMN is much attenuated in sleep, if it can be recorded at all. There are a number of serious methodological problems with each of the studies. The signal-to-noise ratio of the MMN relative to the background EEG is exceptionally small during sleep. The MMN may measure less than 1μV and the background EEG as much as 200-400 μV during Stage 4 sleep. The background EEG will be attenuated by a factor of $\sqrt{n}$ through the averaging process. To attenuate the sleeping EEG to below the amplitude of the MMN may require several hundred trials. Since the deviants are presented rarely, this may not be possible in certain stages of sleep, most notably SWS. Few studies have attempted to record the MMN during REM sleep. REM may be the sleep period in which the MMN could most likely be recorded. The amplitude of the background

EEG is similar to that seen in the "drowsy" state (or Stage 1 sleep). The signal-to-noise ratio is thus much enhanced.

The level of cortical arousal necessary for the MMN to be elicited may also serve as an interacting factor. Studies of drug effects on the MMN have shown that it is enhanced by drugs that heighten cortical activation (Born, Fehm-Wolfsdorf, Lutzenberger, Voigt, & Fehm, 1986; Born, Bother, Pietrowsky, Fehm-Wolfsdorf, Pauschinger, & Fehm, 1987). Similarly, drugs which inhibit cortical arousal decrease the MMN and the amplitude of the N1 (Born, Kern, Fehm-Wolfsdorf, & Fehm, 1987). Born, Bother et al. (1987) suggested that the decreased response was due to a reduced sensitivity of the "non-specific system". Other findings indicate that a high level of cerebral activation may not be a necessary condition for the elicitation of the MMN. Kane, Curry, Butler, and Cummins (1993) were able to elicit a MMN to pitch deviants in some coma patients. Not all of the coma patients however exhibited a MMN. Those individuals who did show evidence of a MMN in coma, had earlier recoveries (i.e., within 48 hrs). Unfortunately, few details of the procedure used in this study were provided. Similarly, sample MMN waveforms were not provided.

REM sleep is associated with a relatively high degree of cortical activation. It may therefore be regarded as an intermediary state on the arousal continuum between wakefulness and NREM sleep. Some studies have indicated that subjects are more likely to behaviourally signal the presence of external stimuli during REM sleep than NREM sleep (Okuma, Nakamura, Hayashi, & Fujimori, 1966; Bonnet, 1982). Burton, Harsh, & Badia (1988) reported that a positive relationship existed between behavioural responding and the presence mental activity in sleep immediately preceding the onset of the stimulus (based on subject's

self-reports upon awakening after the stimulus). A high degree of sleep mentation is likely present in REM, since it is associated with the highest rates of dream recall (Koulack, 1991).

It is possible therefore that subjects may be at least partially conscious of the external environment during REM sleep. In support of this contention, Campbell et al. (1992) observed that the N1 returns to approximately 50% of its waking amplitude during REM. Näätänen (1991) postulated that N1 may subserve "conscious perception of auditory stimuli in general...without indicating what the stimulus is or what its precise features are" (p.212). Thus the occurrence of a deviant stimulus may be registered by the elicitation of an enhanced N1. This is turn may activate the supratemporal MMN response, reflecting the detection of a mismatch with the features of a previous stimulus. If the level of tonic cortical activation is high enough, the amplifying mechanism of the supratemporal MMN may trigger the frontal MMN component, possibly leading to the conscious perception of the stimulus. REM sleep is a period of relative cortical activation (as compared to NREM), and thus the amplifying system may be sufficiently stimulated to generate a small amplitude MMN to the deviant stimuli.

Summary and Rationale

The processing of auditory stimulus change or deviance is reflected in the component structure of the AEP. In waking "ignore" conditions, deviant stimulus presentations may elicit an enhanced N1 complex at approximately 100-150 ms. Deviant-related enhancement of N1 probably reflects the activation of fresh neural elements. Unattended deviant stimuli will also elicit a negativity that, depending on the extent of the stimulus change, may appear

between 100 and 300 ms. This is called N2a or mismatch negativity (MMN). The MMN is elicited by an infrequent stimulus that physically deviates from a frequently presented standard stimulus. In most cases, the MMN (at least to frequency deviants) occurs regardless of attentive state or task demands. If the magnitude of stimulus deviation is large, an additional negativity, labelled N2b, may be superimposed on the descending aspect of the MMN. The N2b may in turn be followed by an associated P3a.

In waking "attend" conditions, the AEP to deviant stimuli is somewhat different. The amplitude of N1 may be enhanced by the superimposition of the attention-related processing negativity. This will be foliowed by an N2 wave comprised of both N2a and N2b subcomponents. N2a or the MMN is elicited automatically as a consequence of the difference between the deviant and standard stimuli. N2b is an attention-related negativity and is usually followed by P3a. If the deviant stimulus is psychologically meaningful, a large late positivity, P3b, will overlap and summate with P3a.

Because of the overlapping and summating effects of a complex of negative and positive waves during attend conditions, most labs prefer to record the MMN when subjects attention is directed away from the standard/deviant stimuli. This is based on the assumption that attention has little effect on the MMN. As has been discussed, this assumption is dubious, at least for MMNs elicited by intensity deviants. For duration deviants, there is a paucity of data. While the assumption appears to be more reasonable for stimuli deviating in frequency, the possibility that subjects inadvertently switch their attention toward the to-be-ignored channel cannot easily be dismissed. Subjects may always be at least partially conscious of the deviant stimulus when they are awake and alert. There may be no means to

resolve this controversy during the waking state. A failure to find a difference in the amplitude of the MMN during attend and ignore conditions can always be attributed to either an independence of attention or an inability to ignore the intrusive stimulus. Since subjects do not make an overt, behavioural response to stimuli presented in the to-be-ignored channel, it is difficult to determine their mental state or degree of conscious awareness. A possible means of resolving this controversy is to record the MMN during states of unconsciousness. This has most often been done during natural sleep.

During NREM sleep, N1 for both deviant and standard stimuli is reduced to near baseline. At sleep onset P2 is increased, but declines to near baseline later in sleep. In REM sleep, the amplitudes of N1 and P2 return to approximately one-half their waking amplitudes. For deviant stimuli, a large negativity emerges in NREM sleep at approximately 350 ms. This N350 may reflect an enhanced, but longer latency, functional analogue to the waking N2b. On the other hand, N350 may reflect a process that is unique to the NREM sleep state. N350 is not evident in REM sleep. Deviants that are abrupt and intrusive may also elicit a late N550-P900 event in NREM called the K-Complex. The K-Complex is not elicited in REM sleep. A number of studies have found evidence for a late positive component in both REM and NREM sleep for large deviants. It is possible that this late positive wave is a functional analogue of the waking P3a. It is unlikely however it is related to the P3b which appears to be abolished in sleep.

In the present thesis, the deviance related AEP component of interest was the MMN. Previous findings concerning the presence of the MMN in sleep are equivocal. Most studies have reported no MMN in NREM sleep although some have reported a small amplitude

MMN in late Stage 2. There is limited evidence of a MMN in REM sleep. These discrepancies are possibly due to methodological inadequacies and the use less than optimal stimulus conditions for MMN elicitation. In addition, studies on the MMN in sleep conducted to date have only examined changes in stimulus frequency. The frequency MMN appears to be least affected by manipulation of conscious state.

Three studies were conducted investigating the presence of the MMN in sleep for different types of stimulus change. In experiment 1, large and small frequency deviant stimuli were presented during wakefulness, REM, and Stages 2 and 4 of NREM sleep. The purpose of this study was to assess the presence of the MMN in sleep the type of stimulus change most often employed in the waking MMN studies. A fast presentation rate and a low deviant probability were used to achieve an optimum MMN response. Both large and small deviance conditions were employed to examine differential effects of sleep on the magnitude of frequency change. The frequency MMN is least affected by manipulation of attention during wakefulness. Thus, if a MMN can be elicited during sleep, it is reasonable to expect that this would occur to a rare auditory frequency changes.

In experiment 2, the duration of deviant stimuli was manipulated. A duration increment and decrement deviant condition were used. Duration deviants have yet to be employed during sleep. The peak latency of the MMN should differ between the two duration conditions. Specifically, the peak latency of the increment MMN should occur later than that for the decrement MMN.

In experiment 3, an intensity deviance condition was used in which intensity increments and decrements deviants were presented during sleep. Previous studies indicated

that the MMN to intensity was the most susceptible to waking attentional influences. It would be expected therefore that the intensity MMN would be markedly influenced by sleep, if it is apparent at all. If it is elicited in sleep, the MMN for intensity may attenuated relative to the MMN for frequency.

Expectations:

1. During the waking state, the MMN should be recorded to frequency, duration and intensity deviants. A true MMN will be largest over fronto-central areas of the scalp and invert in polarity at the mastoid when a nose reference is used.
2. If a MMN can be recorded during sleep, it will be larger during REM than NREM sleep.
3. If a MMN can be recorded during sleep, it will be larger to frequency than either intensity or duration deviants.
4. The MMN to intensity deviants should be most affected by sleep.
5. During sleep, late negativities, such as the N350 will be largest to the most deviant and intrusive of stimuli, the large frequency deviants and the increases in intensity.

Chapter 2

Experiment I: The Mismatch Negativity to Frequency Deviant Stimuli During Natural Sleep

This study is currently "in press" in the journal *Electroencephalography and Clinical Neurophysiology*. Stimuli deviating in auditory frequency were presented during a waking reading condition, and sleep stages 2 (early and late), slow wave (Stages 3 & 4), and REM. In separate conditions, infrequent "large" 2000 Hz and "small" 1050 Hz deviant tones were presented with frequently occurring 1000 Hz standards. Previous studies of selective-attention have shown the MMN for frequency change to be most resilient to attentional influence. It was expected therefore that, if the MMN could be recorded during sleep, it would most likely be elicited by frequency deviant stimuli. The MMN has also been shown to increase in amplitude and decrease in peak latency for wider magnitudes of stimulus change. Therefore, the MMN elicited by the large frequency deviants was expected to be larger and have a shorter latency than that for the small deviants. Previous findings indicate that the MMN is attenuated under conditions of lowered cortical arousal. If the MMN is elicited in sleep, it should therefore be larger in REM than NREM sleep.

Introduction

When a subject is presented with a deviant stimulus occurring in a train of repetitive "standard" stimuli, a "mismatch negativity" (MMN) is elicited. The MMN is a negative wave typically beginning at about 100 ms and lasting up to 300 ms after stimulus onset. MMNs to spatial auditory changes have however been observed to begin as early as 50 ms (Paavilainen et al., 1989). The MMN has been shown to be elicited by auditory stimuli deviating with respect to tonal frequency (Näätänen et al., 1978; Sams, Paavilainen et al., 1985), intensity (Näätänen et al., 1987), duration (Näätänen et al., 1989) spatial location (Paavilainen et al., 1989), inter-stimulus interval (Ford & Hillyard, 1981; Nordby et al., 1988) and complex phonetic changes (Aaltonen et al. 1987; Sams et al., 1990). The amplitude of the MMN is determined by the degree of deviance, the probability of the deviant stimulus, and the rate of stimulus presentation (Näätänen, 1992).

Early research indicated that the amplitude of the MMN was independent of task demands or the subject's level of attention (Näätänen et al., 1978; Sams, Paavilainen et al., 1985). Subsequent studies have indicated that when attention is strongly focused on input into one ear, the MMN to intensity deviants in the unattended ear may be reduced in amplitude (Woldorff, et al., 1991). Näätänen et al. (1993) have also reported that attention can modulate the intensity-elicited MMN when stimuli are presented at very rapid rates of presentation. In contrast, the elicitation of the frequency MMN appears to be much less affected by attention (Näätänen et al.,1993). A recent report however suggests that even the frequency MMN can be attenuated by strongly focused attention (Trejo et al., 1995).

The issue of attention and the MMN is confounded by the fact that it may be impossible for awake and alert human subjects to completely ignore auditory input even in the highly demanding selective-attention conditions (Campbell et al., 1992). Sleep is the period of time when subjects are least conscious of the external environment. A limited number of laboratories have attempted to record the MMN during sleep. Csépe et al. (1987) were able to record a reduced amplitude MMN during paradoxical (or REM) sleep in cats. Alho et al., (1990) observed a large MMN to frequency deviance in human newborns during "quiet" sleep when a fast rate of presentation was employed. In sleeping adult humans, Paavilainen et al. (1987) failed to record a MMN to a small frequency change (1000 Hz vs 1050 Hz) during non-REM (NREM) sleep in the early portion of the sleep period. Campbell et al., (1992) used a much wider frequency change (1000 Hz vs 2000 Hz) and observed a small amplitude MMN during stage REM of sleep. Their rate of presentation (ISI = 2.0 s) was, however, not optimal for the recording of the MMN. Recently, Winter et al. (1995) reported an absence of a MMN to large and small pitch deviants in Stage 2 sleep. Sallinen et al. (1994), using a very rare deviant probability, did observe a MMN in Stage 2 sleep but only on trials in which a K-Complex was elicited. They were unable to record a MMN during sleep stages 1, 4 and REM.

The purpose of the present study was to determine if a MMN could be recorded from sleeping adult subjects by using optimal stimulus conditions for eliciting the MMN such as a rapid presentation rate and a wide frequency separation. Auditory stimuli deviating in tonal frequency were presented during both REM and NREM sleep. A frequency change was used because it appears to be minimally affected by the subject's level of conscious awareness.

Methods

Subjects

Eight female undergraduate students (aged 19-24; mean = 20.3 years) slept for a single night in the sleep laboratory. All subjects were self-described "good sleepers" who reported no history of neurological or psychiatric disorder. All were tested for normal hearing (15 dB ISO) at 500, 1000, 2000 and 4000 Hz. They were asked to refrain from alcohol and caffeine use for 24 hours prior to the study. Subjects provided written informed consent prior to participation and were offered an honorarium as compensation.

Procedure

Two different "oddball" stimulus conditions were run: (1) Large deviance: 1000 Hz standard with 2000 Hz deviant tones, (2) Small deviance: 1000 Hz standard with 1050 Hz deviant tones. Stimuli were 80 dB SPL tone bursts of 55 ms duration with a rise-and-fall time of 5 ms. The inter-stimulus interval was 0.6 s. The probability was 0.8 for standards and 0.2 for deviants. A single block of 500 trials was created for each of the large and small deviance conditions, with deviant tones always separated by at least one standard tone.

The auditory stimuli were transduced by a specially designed over-the-ear hearing-aid containing a Knowles ED-197 wide bandpass speaker. The output of the speaker was conducted through 4 cm of no. 13 standardized plastic tubing (1.93 mm in diameter) attached to an individually fitted ear mould which was placed into the right ear of the subject. The right ear was selected because most subjects preferred sleeping on their left side. The hearing-aid device assured constancy of stimulus input to the ear of the subject in spite of the

movements that might have occurred during the all-night sleep session. The system's response was calibrated using a Bruel and Kjaer 2209 sound level meter and a 2 cm^3 acoustic coupler.

Recordings were conducted in an acoustically and electrically shielded sleep chamber. Waking data were collected while subjects read a book and thus ignored the auditory stimuli. Recordings were also made while subjects slept throughout the night. The two stimulus conditions were presented during definite stages 2, 4 and REM sleep (as defined by the criteria of Rechtschaffen and Kales, 1968). Stage 2 was subdivided into "early" and "late" halves to examine possible time-of-night differences. An attempt was made to repeat all conditions three times during the waking and sleeping states in order to ensure replicability of results. For some subjects, there was insufficient time to permit full replication of a block of trials. In cases of sleep stage ambiguity, the condition was rejected from further analysis. Stimulus presentation was discontinued and rejected when the EEG pattern indicated a sleep stage change or upon subject arousals or movements.

Physiological Recording

EEG and EOG were recorded using Grass gold electrodes attached to the scalp with collodion-soaked gauze. EEG electrodes were placed at midline frontal, central, and parietal (Fz, Cz, Pz) sites. Electrodes were also placed at three equidistant lateral sites located on a line extending from Fz to the left mastoid. These were labelled L1, L2, and L3 (left mastoid). The reference for all EEG sites was the tip of the nose. When a nose reference is used, a true MMN should reverse in polarity at the mastoid (or L3) site (Alho et al., 1986).

Although the MMN is slightly larger over the right hemisphere (Giard et al., 1990), electrodes were placed over the left scalp since stimuli were presented to the contralateral (right) ear. Paavilainen et al. (1991) reported that the right hemisphere dominance of the frequency MMN was marginal.

The EOG was recorded from an electrode placed one centimetre above the outer canthus of one eye referenced to another electrode placed one centimetre below the outer canthus of the other eye. This permitted the recording of both vertical and horizontal eye movements on a single polygraphic channel. The EEG and EOG were recorded with a high frequency setting of 35 Hz and a time constant of 2.0 s. Inter-electrode impedance was below 5 kOhms. The EEG and EOG signals were also written out on paper at a speed of 10 mm/s for purposes of sleep staging.

The EEG and EOG sweep began 50 ms prior to stimulus onset and continued for another 500 ms following it. A total of 256 data points were digitized for each channel (i.e., a sample was taken every 2.15 ms). Single trials were stored on hard disk for later off-line analysis. During wakefulness, trials in which the EOG or EEG exceeded $\pm$ 100 μV were rejected from the average. During sleep, the artifact reject was set to $\pm$ 150 μV to accommodate the high amplitude frontal K-Complexes often seen in NREM and eye movement artifact (horizontal or vertical) seen in REM sleep. The standard and deviant average waveforms for each condition were digitally filtered using a bandwidth of 3-12 Hz (3 dB roll-off). The purpose of the digital filtering was to attenuate the effects of large slow delta waves in sleep which overlapped the MMN latency range.

Statistical Analysis

The MMN is best observed in a "difference" wave. Difference waveforms were computed by subtracting, point-by-point, the standard from the deviant waveforms at each electrode site in the same condition. The 500 ms sweep period was subdivided into ten 50 ms latency intervals starting at stimulus onset. Within each of these intervals, the average of all data points was computed, yielding an average amplitude measure. A similar scoring method has been used by Näätänen and his colleagues (see for example, Alho et al., 1986 and Alho et al., 1989).

The actual determination of a MMN within sleep is not without statistical difficulties. A simple approach would be to compare waking and sleeping MMNs. However, a failure to find a difference does not imply the *presence* of a sleeping MMN. Similarly, the fact that the amplitude of the waking and sleeping MMNs might be different does not imply the *absence* of the MMN within sleep.

Confidence intervals were therefore computed for each of the ten latency intervals to determine if a MMN could, in fact, be recorded in each stage of sleep. This procedure determined whether the probability of the mean value of a particular interval fell within an upper or lower range. If the lower limit was significantly less than 0 μV (i.e., was negative), the interval was considered to contain an MMN. This procedure is equivalent to computing a t-test between the deviant and standard waveforms (Winer, 1971). Because a negative directionality was predicted (i.e., the polarity of the MMN should be negative), a one-tailed test of significance ($p < .05$) was applied to the confidence intervals. To restrict the likelihood of a chance finding, the scalp distribution of the negative deflection had to

conform to that observed in the literature. Thus the frontal or central deflections had to be larger (more negative) than the parietal. In addition, the MMN had to occur within a 100-350 ms time window. Finally, the difference wave had to reverse polarity at L3 (i.e., the left mastoid). Only after the existence of a MMN was determined within the different stages of sleep were statistical comparisons (two-tailed t-tests for dependent groups) between the sleep and waking stages carried out. All differences were considered to be significant at $p < .05$.

Results

Large Deviance

The superimposed grand-averaged waveforms to the standard and deviant stimuli for all subjects in the large deviance condition are presented in Figure 2.1. When subjects were awake, a distinctive N1-P2 complex was identified. The N1 and P2 following both standard and deviants peaked at 98 and 165 ms respectively. The difference waves (deviant minus standard) appear in the lower portion of the figure. A clear MMN was evident in the difference waves for the Awake condition between 100 and 200 ms. At the mastoid, it was below baseline (i.e., reversed polarity) in the same intervals. The mean vertex amplitudes of the difference waves are presented for each interval in Table 2.1. The deviant-standard difference was significantly above baseline ($p < .05$) in both the 101-150 and 151-200 ms intervals after stimulus onset.

The findings pertaining to REM sleep are based on only seven subjects because there

was insufficient REM data from one subject to permit averaging. During REM, N1 was above baseline, attaining approximately 60% of its waking amplitude and showing a peak latency approximately 20 ms later. The difference waves indicated the presence of a fronto-central MMN in REM which overlapped the peak of the N1. In addition, L3 showed a polarity reversal in this interval. The vertex MMN was significantly above baseline in the 101-150 ms interval (see Table 2.1). The MMN observed in REM was significantly reduced by approximately 30% compared to the waking MMN ($p < .01$). In the NREM sleep stages (Stage 2 - early, Stage 2 - late, & Stage 4), N1 was near or below the baseline level. A small negativity was evident in the difference waves for both early and late Stage 2. These negative waves occurred in the expected MMN latency range and were associated with polarity reversals at L3. However, none of these negativities reached statistical significance.

---------- Insert FIGURE 2.1 & TABLE 2.1 About Here ----------

Small Deviance

The grand-averaged waveforms to the standard and deviant stimuli for all subjects in the small deviance condition are presented in Figure 2.2. In wakefulness, a clear N1-P2 complex, peaking at 98 and 155 ms respectively was evident for both standards and deviants. A small but significant MMN was observed in the difference waves for the Awake condition in the 151-200 ms interval. The mastoid (L3) also showed a polarity reversal in this interval. The mean vertex amplitude of the difference waves for each interval are presented in Table 2.2. The MMN peaking in the 151-200 ms interval was significant ($p < .05$), but

was smaller in amplitude relative to that observed in the large deviant condition. In REM sleep, an N1-P2 complex was again apparent, but N1 peak latency was prolonged by 25 ms compared to wakefulness. A significant MMN ($p < .05$, see Table 2.2) was observed in REM over the fronto-central sites. This MMN peaked unusually early during the 101-150 ms interval. Its amplitude was not significantly different from the waking condition. The mastoid (L3) again showed a polarity inversion. For early Stage 2, a statistically significant negativity was apparent in the difference wave but it was too early to be a MMN (i.e., it peaked prior to 100 ms) and did not show a polarity reversal at L3. A small amplitude MMN-like was identifiable during late Stage 2 but its amplitude was not significantly greater than the baseline level. No MMN-like wave was apparent in Stage 4 sleep.

---------- Insert FIGURE 2.2 & TABLE 2.2 About Here ----------

In both the large and small deviance conditions, other statistically significant negativities were also obtained (see Tables 2.1 & 2.2). For example, a large negativity in Stage 4 for large deviants occurred between 301 and 400 ms. However, these additional negativities peaked beyond the expected MMN latency range and were not associated with a polarity reversal at the mastoid location.

The difference waves for the Awake and REM conditions are superimposed in Figure 2.3 to facilitate examination of the temporal and distributional features of the MMN to both the large and small deviants. For large deviants, the MMNs in REM and wakefulness showed similar onset latencies, but the duration of the waking MMN was approximately 50

ms longer than for REM. In contrast, the small deviant data showed an onset latency for the MMN in REM that was approximately 50 ms earlier than in wakefulness, and an absence of the later negativity observed for the large deviants.

---------- Insert FIGURE 2.3 About Here ----------

Post-hoc dependent groups t-tests were performed to compare the midline scalp distribution of the MMN in REM with that of wakefulness for the 100-150 ms interval. The waking MMN to large deviants was maximal at Cz (-1.58 μV). It showed a non-significant decline at Fz (-0.79 μV), but showed a significant reduction at Pz (-0.09 μV, $p<.05$). The MMN in REM to large deviants was also maximal at Cz (-1.12 μV) and was reduced at Fz (-0.81 μV) and at Pz (-0.32 μV) but these differences were not significant. For small deviants, the waking MMN was again maximal at Cz (-0.69 μV) with a non-significant reduction at Fz (-0.54 μV) and a significant decrease at Pz (-0.03 μV, $p<.05$). In REM, the MMN was also largest at Cz (-1.11 μV) but showed significant reductions at both Fz (-0.70 μV, $p<.05$) and Pz (-0.05 μV, $p<.05$).

Discussion

A MMN to both large and small frequency changes was elicited when subjects were awake and reading. The MMN in the small deviance condition was reduced in amplitude relative to that of the large deviance condition but had a similar peak latency. The most

novel finding of this study was the detection of a MMN to both large and small frequency changes during REM sleep. For the large deviant condition, the MMN in REM had a peak latency similar to wakefulness (100-150 ms) but was reduced in amplitude by about 30%. For the small deviance condition, the MMN in REM had an earlier peak latency and an amplitude that did not significantly differ from the waking condition. This is consistent with the findings of Campbell et al. (1992) who found an unusually early MMN in REM sleep to pitch changes, although they reported that the amplitude was attenuated. Csépe et al. (1987) also reported a MMN in the REM-like sleep state of cats. The scalp distribution of the waking and REM-recorded MMNs were also similar. In wakefulness and REM, the MMNs to both large and small deviants showed a maximum amplitude at the vertex, with a small decrease in amplitude at the frontal electrode, and a large amplitude reduction at Pz.

No MMN was identifiable in any of the NREM sleep stages for either large or small deviants. In both frequency conditions, a small negative-going wave, occurring between 50 to 150 ms, was observed in late Stage 2. This negativity was not, however, significantly different from baseline. Moreover, the MMN following the small deviant did not invert in polarity at the mastoid. Sallinen et al. (1994) reported that the MMN can be recorded during Stage 2 sleep but only if the deviant stimulus also elicited a K-Complex. In the present study, the deviants did not elicit enough K-Complexes to permit averaging. In the study by Sallinen et al. (1994), deviant probability was unusually low (0.02). Therefore, on average, the time between deviants was quite long. In the present study, deviants occurred on 20% of the trials (i.e., an average of one every 3 s). Bastien and Campbell (1994) have indicated that the elicitation of the K-Complex is highly dependent on the rate of stimulus presentation.

K-Complexes are rarely elicited when the time between stimuli is less than 10 s. Nevertheless, it is possible that the presence of the small amplitude MMN during Stage 2 may be a result of collapsing across relatively few trials containing a K-Complex and several trials not containing it.

Significant negativities were also found in the difference waveforms in REM and NREM sleep stages beyond the expected 100-300 ms MMN latency range. Other authors have also reported negativities occurring at about 300-350 ms to deviant auditory stimuli presented in sleep (Harsh, et al., 1994; Nielsen-Bohlman, et al., 1991; Salisbury et al., 1992; Winter et al., 1995). However, given the long latency of such components they are probably not reflections of a true "mismatch" process. Rather, they may represent the "intrusion" of a limited number of K-Complexes into the averaging process. The K-Complex consists, in part, of two large negative peaks, one occurring at approximately 350 ms and the other at approximately 550 ms (Bastien & Campbell, 1992 ; Halász et al., 1985). In the present study, smaller amplitude negative waves (i.e., those below the 150 μV rejection cut-off), occurring at approximately 350 ms, may have been included in some of the averages.

The MMN was attenuated in REM sleep following the large deviant stimulus. This may be explained by the dual component process theory of MMN generation proposed by Näätänen (Näätänen, 1991; Näätänen et al., 1993). This theory assumes the existence of two types of neuronal fields responsible for the generation of the supratemporal component of the MMN. The first, referred to as *computational* neurons, are responsible for the elicitation of the MMN. The second type are *amplifying* neurons which determine the magnitude of the response. The activity of the amplifying neurons account for variations in MMN amplitude

related to stimulus attributes (frequency, amplitude, etc.) and vigilance states (attention, drug effects, etc.). In REM sleep, the obligatory response of computational neurons appears to remain active but the effects of amplifying neurons are attenuated. The result is a reduced amplitude MMN in REM, an effect observed in this study for large frequency deviants only.

This interpretation does not necessarily account for the earlier termination of the REM-recorded MMN. The fronto-central MMN to the large deviants during the waking state was significantly above baseline from 100 to 200 ms. The later portion (151-200 ms) was not present during REM. The MMN has been divided into at least two distinct sub-components differing with respect to latency and scalp distribution (Giard et al., 1990; Näätänen & Michie, 1979). The first component is an early, sensory-specific, contralaterally larger wave believed to be generated around the auditory cortex. The second component is a later, non-specific frontal wave. Näätänen and Michie (1979) hypothesized that the sensory-specific mechanism involves the preconscious detection of stimulus deviation which then serves to activate frontal mechanisms related to the conscious discrimination of stimulus deviance. Differential activation of these underlying generators might account for variation between the REM and waking MMNs. Specifically, the attenuation of the later portion of the MMN in REM may be attributed to a deactivation of the frontal generators. This would suggest that only the early temporal components remain active in REM sleep while the later, frontal mechanisms fail to be activated. Thus, sensory discrimination of stimulus deviance might persist in REM, but the subsequent capacity for conscious perception of stimulus deviance might not.

Another explanation for the longer duration negativity seen in wakefulness for large

frequency deviants is that it represents an N2b component. The N2b is usually elicited by input to an attended channel (Näätänen & Gaillard, 1983). A smaller amplitude N2b may however be observed in non-attend conditions for deviant stimuli that are particulary difficult to ignore (Näätänen et al., 1982) or that are "perceptually obtrusive" (Loveless, 1986). Perceptual intrusions would be more probable when the difference between the standard and deviant is large. The finding of a second N2b component for the large but not the small deviant is consistent with this hypothesis.

The *apparent* latency shift for small deviants in REM relative to the waking condition might be explained by the presence of an enhanced signal-to-noise ratio in REM. In comparison to the sleeping subject, the awake subject might experience both greater external (environmental) and internal (psychological) "noise". Thus, the processing of a more difficult discrimination in the form of a small frequency separation may have been facilitated in REM sleep, compared to wakefulness.

A number of authors have pointed to the functional similarity between the REM and the waking states. For example, Horne (1988) noted that hippocampal theta activity is evident during wakefulness and REM sleep (but not during NREM) and appears to be related to the directing of "attention" toward novel stimuli. Associations have also been made between REM sleep and the function of memory consolidation (Crick & Mitcheson, 1983; Horne & McGrath, 1984; Smith & Lapp, 1991). It is possible that REM sleep resembles wakefulness in the way new information is encoded or processed. Comparison or mismatch detection processes may remain at least partially functional during this period of sleep.

Why was there no MMN in Stage 4 sleep even when liberal, one-tailed t-tests were

used to test for significance? Paavilainen et al. (1987) also did not observe a MMN in Stage 2 or Stage 4 of sleep. They however used a small frequency separation. Campbell et al. (1992) also failed to observe a MMN in either Stage 2 or Stage 4 sleep. While their frequency separation was large, their rate of stimulus presentation was long. In the present study, optimal conditions, including a wide frequency separation and a rapid rate of presentation, were used yet the MMN still could not be recorded. Similarly, Sallinen et al. (1994) also failed to observe a MMN during Stage 4 using optimal recording conditions. Previous studies have tended to employ conservative non-directional statistical procedures. Only a large MMN would therefore have attained significance. In the present study, liberal statistical procedures were used and the MMN could still not be recorded. It is thus possible that both the computational and amplifying neuronal populations of the MMN are not active in NREM. This would contradict the view that the MMN is elicited regardless of the level of consciousness. On the other hand, Kane et al. (1993) reported the elicitation of a MMN to pitch deviant tones in some coma patients. Those patients who exhibited the MMN had earlier recoveries from coma (i.e., within 48 hours) than those who did not. Unfortunately the authors did not present data concerning the amplitude, latency or scalp topography of the coma-recorded MMN. Moreover, a description of the background EEG was not provided. It is possible that the EEG of those patients in whom a MMN could be recorded was closer to that of a waking state than those in whom the MMN could not be recorded. The fact that these patients returned to a waking state within 48 hours provides support for the hypothesis of differential EEG. Nevertheless, the findings do suggest that the MMN can be recorded in some "unconscious" states.

Näätänen (1992) proposed that the MMN mechanism is reflective of a sensory memory trace (or "buffer") of the auditory stimulus. The duration of the memory trace is relatively short. This explains why the MMN is easiest to elicit with rapid rates of presentation. During NREM sleep, it is possible that the sensory memory for the standard stimulus dissipates within the 600 ms inter-stimulus interval. This would, however, be incongruent with the waking state for which the duration of the auditory store has been estimated to be up to 10 s (Sams et al., 1993). The probability of deviant occurrence was 0.2 in the present study. This is unusually high but was selected as a compromise to provide a sufficient number of deviant trials to remove the very high background EEG accompanying NREM sleep. It may be that only very infrequent deviant stimuli will elicit a MMN in Stage 4 sleep. This does not appear to be the case. Sallinen et al. (1994) failed to observe a MMN in Stage 4 when deviant probability was extremely low (0.02).

It is possible that the MMN is dependent on the presence of N1. Näätänen (1991) hypothesized that the N1-generating process might subserve conscious perception of the auditory stimulus. Campbell et al. (1992) also arrived at a similar conclusion since the amplitude of the N1 gradually declines during sleep onset and dissipates during NREM sleep. During REM, both the N1 and MMN can be elicited although they may be attenuated. Similarly, drugs that increase cortical arousal appear to enhance the amplitude of the MMN (Born et al., 1987a). By contrast, drugs that decrease cortical arousal tend to attenuate both the MMN and the amplitude of the N1 (Born, et al., 1987b). In this study, the attenuating effects were attributed to a reduced sensitivity of the non-sensory system (perhaps the frontal component of both the N1 and MMN; see also Giard et al., 1994). N1 and the MMN do not

always covary. As the rate of stimulus presentation increases, the amplitude of the N1 decreases. The MMN, however, increases in amplitude. Indeed, the rate of presentation can be so fast as to make N1 difficult to detect, yet the MMN remains quite large (Näätänen et al., 1987). Particularly damaging to this hypothesis is the fact that the MMN can be elicited by stimulus conditions involving deviant duration decrements and partial stimulus omissions (for a review, see Näätänen, 1992). In such stimulus omissions, N1 is not evoked.

The absence of the MMN during NREM sleep may also be explained by the overlapping spatial and temporal influence of the large slow waves which typify the tonic EEG. The effects of the slow waves on the ERP may be attenuated using digital filtering techniques. We found that a very sharp high-pass filter of 4.0 Hz was necessary to observe even the smallest MMN-like wave in slow-wave sleep. The use of such an extreme filter however caused a significant distortion of the waking MMN, and removed the polarity inversion at the mastoid.

	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450	451-500
AWAKE	0.24 (0.63)	-0.24 (0.48)	-1.58* (1.82)	-1.33* (1.28)	0.67 (1.56)	1.45 (1.35)	0.23 (1.51)	0.07 (1.90)	-0.13 (1.36)	-0.41 (0.63)
STAGE 2 Early	-0.01 (0.65)	0.08 (1.32)	-0.26 (1.10)	0.14 (1.65)	0.63 (0.92)	0.41 (1.08)	-0.69 (1.36)	-0.19 (1.78)	0.68 (0.98)	-0.01 (0.65)
STAGE 4	0.23 (1.05)	-1.13 (2.74)	0.44 (2.00)	0.57 (1.58)	0.85 (0.08)	0.08 (1.40)	-2.00* (1.12)	-1.54* (1.62)	-1.50 (3.12)	0.23 (1.05)
STAGE 2 Late	-0.10 (0.94)	-0.44 (1.37)	-0.21 (1.16)	0.29 (1.06)	0.21 (1.32)	0.40 (0.86)	-0.68 (1.18)	-0.42 (1.49)	-0.20 (1.37)	-0.10 (0.94)
REM	-0.19 (0.67)	-0.22 (1.95)	-1.12* (1.09)	0.21 (0.52)	0.81 (1.35)	0.17 (1.92)	-0.10 (1.80)	-1.05* (0.67)	-0.60 (0.68)	-0.04 (0.67)

Table 2.1

Large deviance: Mean vertex amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 500 ms sweep. For all conditions n=8, except for REM where n=7. * denotes negative amplitude values that were significantly different from baseline ($p < .05$).

	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450	451-500
AWAKE	-0.45 (0.81)	-0.34 (1.85)	-0.69 (0.62)	-1.04* (1.22)	0.41 (0.74)	-0.24 (1.38)	-0.18 (1.31)	-0.61 (1.56)	-0.48 (1.54)	-0.49 (0.81)
STAGE 2 Early	-0.84 (1.10)	-1.20* (0.96)	0.23 (1.25)	0.47 (1.54)	0.20 (1.37)	-0.05 (1.24)	-0.67 (1.06)	-1.06 (2.00)	-1.36 (2.12)	-0.31 (1.17)
STAGE 4	0.53 (0.98)	0.35 (1.29)	0.28 (1.10)	0.93 (1.64)	0.16 (0.86)	-0.49 (0.97)	-0.77 (0.98)	-0.46 (1.56)	-0.08 (1.51)	0.46 (0.72)
STAGE 2 Late	0.10 (0.88)	-0.41 (1.21)	-0.45 (0.73)	0.22 (1.21)	0.60 (1.19)	0.36 (1.01)	0.28 (1.51)	-0.02 (1.12)	-0.28 (1.99)	0.14 (0.58)
REM	-0.31 (0.87)	-0.61 (1.45)	-1.11* (1.02)	-0.66 (1.34)	-0.37 (2.03)	-0.02 (0.38)	-0.05 (1.17)	-0.16 (1.50)	-0.88* (0.81)	-0.88* (0.87)

Table 2.2

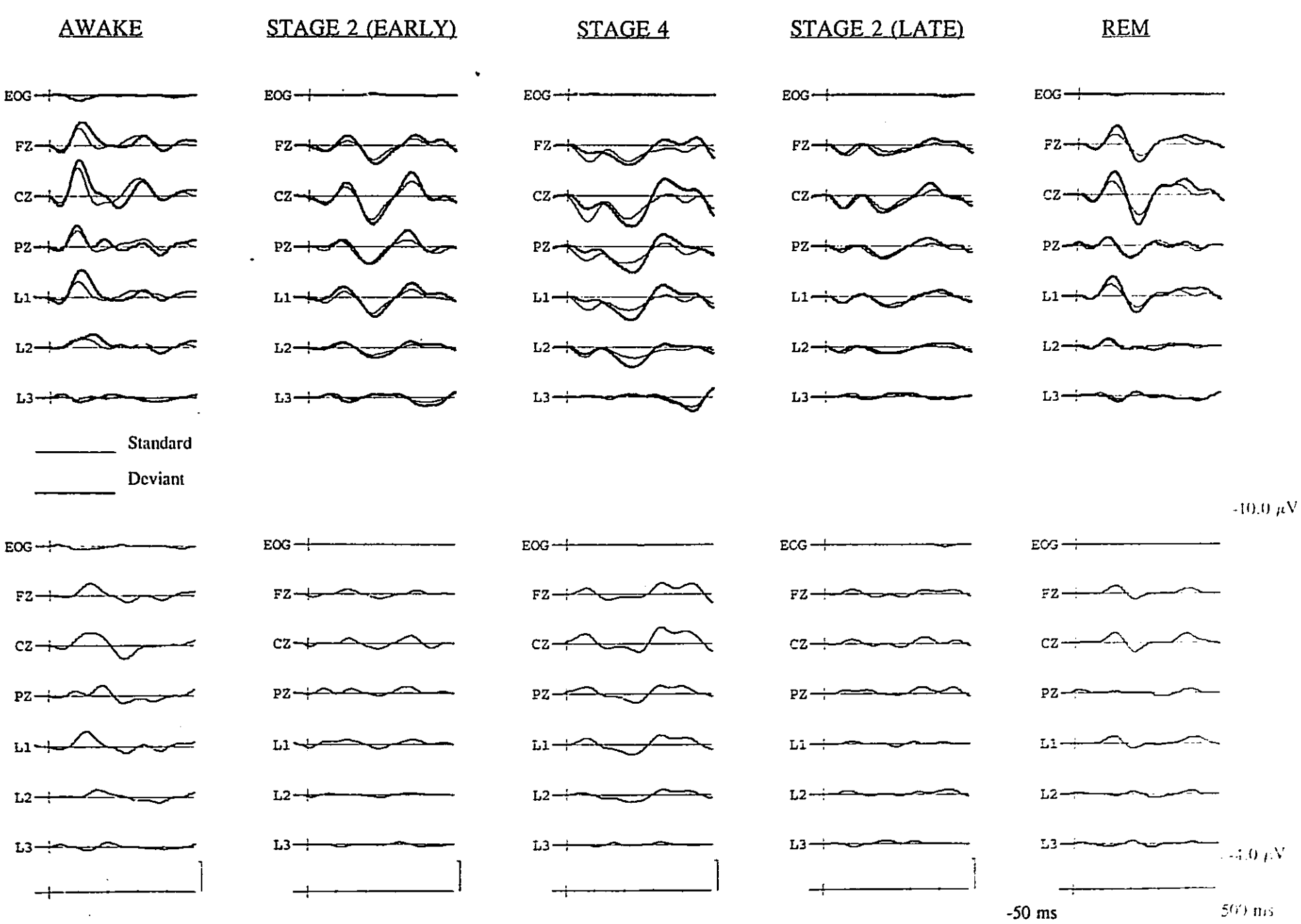
Small deviance: Mean vertex amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 500 ms sweep. For all conditions n=8, except for REM where n=7. * denotes negative amplitude values that were significantly different from baseline ($p < .05$).

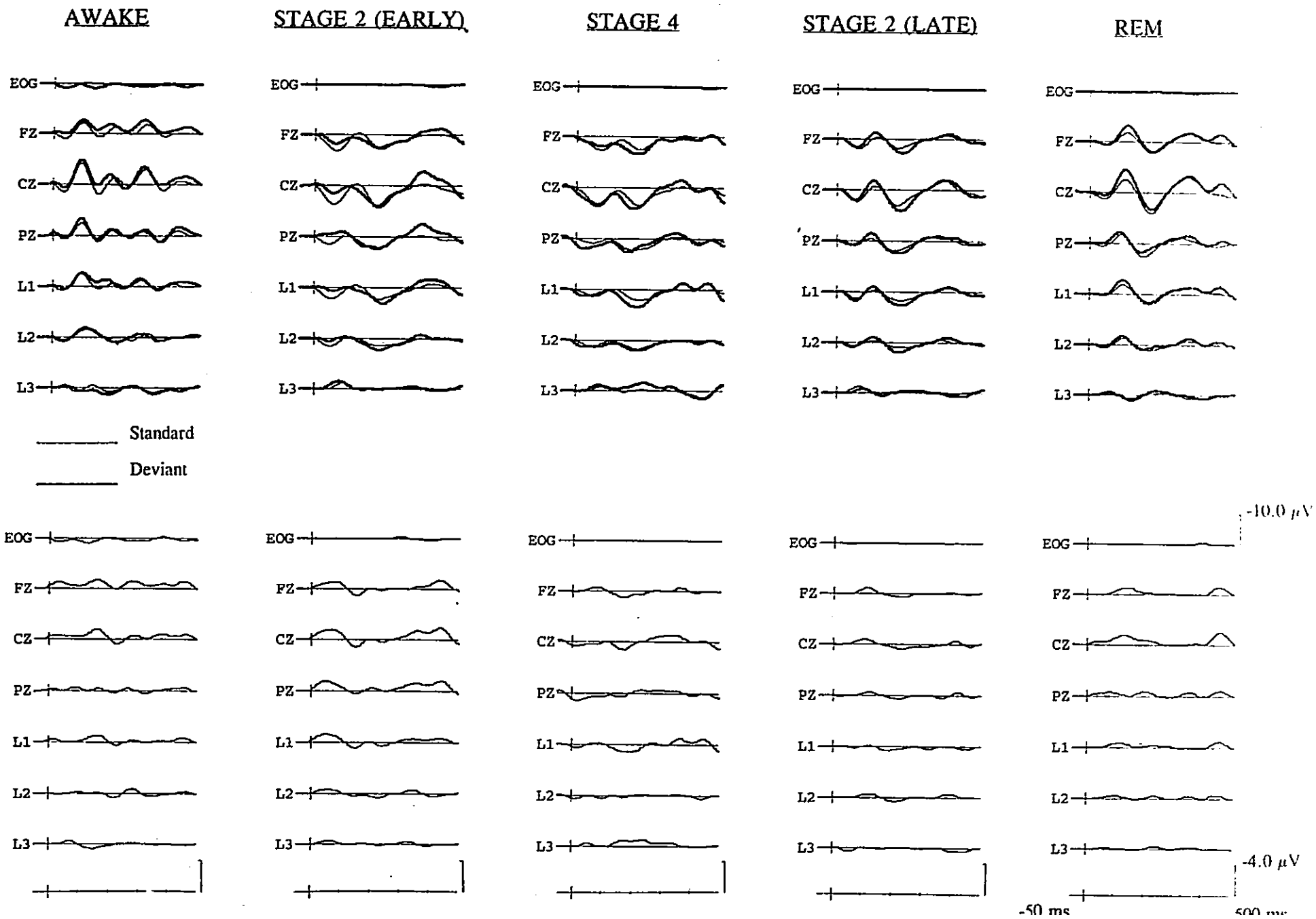
Figure Legend

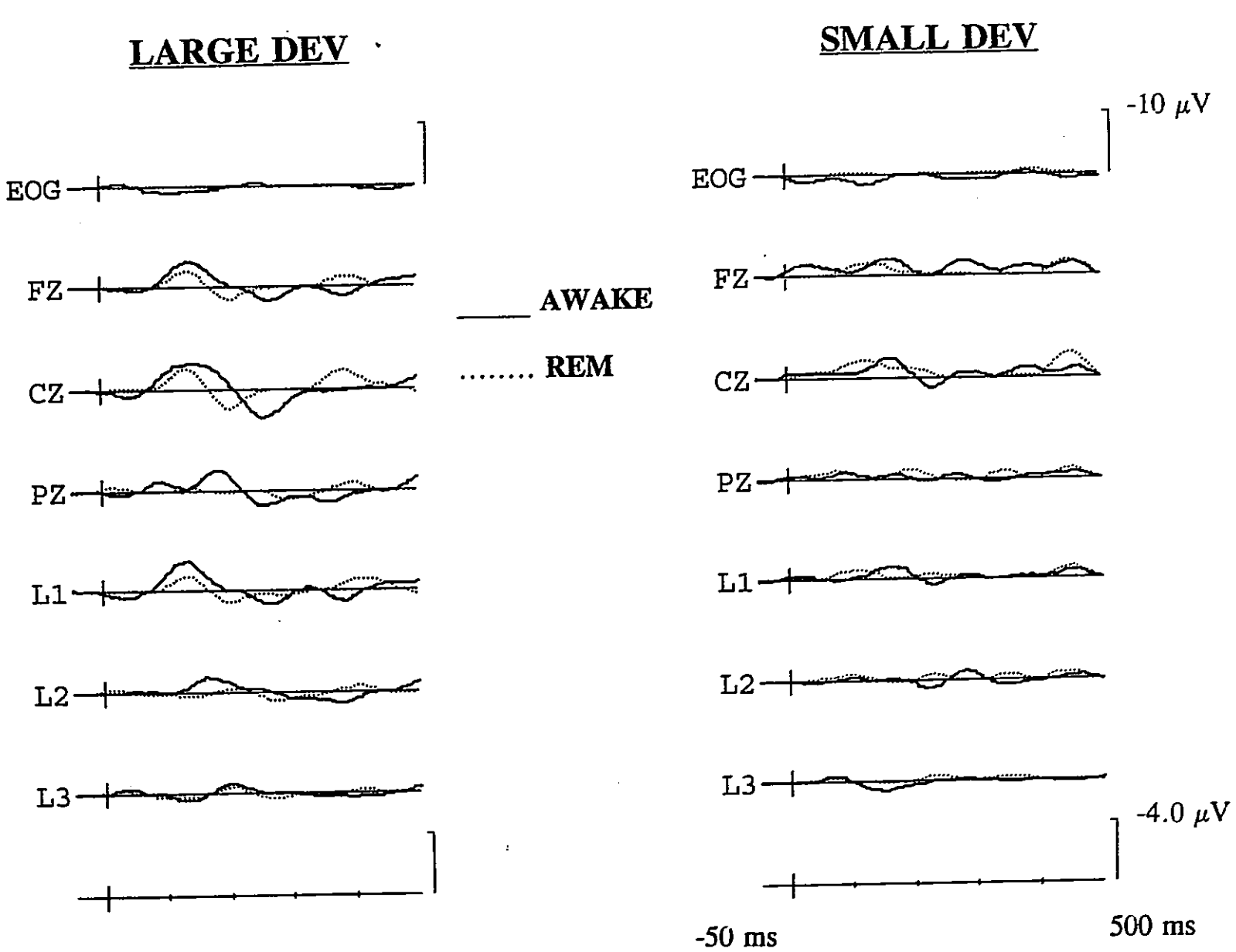
Figure 2.1. Deviant (2000 Hz) and standard (1000 Hz) grand average waveforms for Awake, early Stage 2, late Stage 2, Stage 4 (n=8), and REM (n=7). Deviant-standard difference waveforms appear in the lower portion.

Figure 2.2. Deviant (1050 Hz) and standard (1000 Hz) grand average waveforms for Awake, early Stage 2, late Stage 2, Stage 4 (n=8), and REM (n=7). Deviant-standard difference waveforms appear in the lower portion.

Figure 2.3. Difference waves (deviant - standard) for Awake and REM for large (2000 Hz) and small (1050 Hz) deviant conditions.


AWAKE
STAGE 2 (EARLY)
STAGE 4
STAGE 2 (LATE)
REM
EOG
FZ
CZ
PZ
L1
L2
L3
Standard
Deviant
-10.0 μV
-50 ms
500 ms


AWAKE
STAGE 2 (EARLY)
STAGE 4
STAGE 2 (LATE)
REM
EOG
FZ
CZ
PZ
L1
L2
L3
Standard
Deviant
-10.0 μV
-4.0 μV
-50 ms
500 ms


LARGE DEV
SMALL DEV
-10 μV
EOG
FZ
CZ
PZ
L1
L2
L3
AWAKE
REM
-4.0 μV
-50 ms
500 ms

Chapter 3

Experiment II: The Mismatch Negativity During Natural Sleep: Duration Deviants

This study is currently "in preparation" for submission to the journal *Electroencephalography and Clinical Neurophysiology*. Auditory stimuli deviating in duration were presented during a waking reading condition and sleep stages 2 (early & late), SWS and REM. In separate conditions, infrequent 150 ms "increment" and 50 ms "decrement" deviant tones were presented with frequently occurring 100 ms standards. In the previous study (Chapter 2), frequency deviant stimuli elicited a negativity in REM sleep that conformed to the latency and scalp distribution criteria established in the literature for the MMN. It has been shown elsewhere however that deviant auditory stimuli may elicit other forms of negativities in sleep such as N1 in REM sleep and possibly N350 in REM and NREM sleep. The MMN may be dissociated from these other deviant-related negativities by employing a stimulus condition in which the duration of stimuli is manipulated. The MMN is dependent upon the comparison of the physical features of the deviant with the preceding standard. Therefore, if the duration of the standard is held constant, a long duration deviant will elicit a later MMN than a short duration deviant. This shift in latency would not be observed for N1 or N350. Thus the purpose of this study was to determine if a MMN observed in sleep would demonstrate this "latency shift". The use of a short duration deviant condition would also demonstrate that the negativity is not due to the "sustained potential" which is elicited by longer duration stimuli.

Introduction

A deviant auditory stimulus occurring infrequently in a background of frequent homogeneous stimuli elicits a component of the human auditory event-related potential (ERP) called the "mismatch negativity" (MMN). In awake and alert subjects, the MMN typically appears as a negative wave overlapping the N1-P2-N2 complex of waves at approximately 100-300 ms. The MMN has been observed however to commence as early as 50 ms (Paavilainen et al., 1989). The MMN may be elicited by many types of auditory stimulus changes including tonal frequency (Näätänen et al., 1978; Sams et al., 1985; Alho et al., 1994), intensity (Näätänen et al., 1987; Woldorff et al., 1991; Näätänen et al., 1993), duration (Näätänen et al., 1989; Paavilainen et al., 1991), and phonetic structure (Aaltonen et al., 1987). The amplitude of the MMN increases and its peak latency decreases for greater magnitudes of stimulus deviation (Sams et al., 1985; Paavilainen et al., 1989).

Early research indicated that the subject's level of attention or consciousness did not affect the morphology of the MMN (Näätänen et al., 1978; Sams et al., 1984; Sams et al., 1985). This assumption has been the focus of an active debate in the literature (see for example, Woldorff et al., 1991; Näätänen, 1991; Näätänen et al., 1993). Some laboratories have investigated this issue by recording the MMN in states of unconsciousness, most notably during natural sleep. The majority of sleep studies have attempted to record the MMN to frequency deviants. There appears to be a general consensus that the frequency MMN cannot be elicited in non-REM (NREM) sleep (Paavilainen et al., 1987; Campbell et al., 1992; Winter et al., 1995) except perhaps in association with the K-Complex (Sallinen et

al., 1994).

In a recent study, Loewy et al. (in press) reported the appearance of an attenuated but statistically significant deviant-related negativity during REM sleep following frequency deviants. This negativity was elicited by both large and small frequency separations and was not apparent in NREM stages of sleep. The authors argued that this REM-related negative wave was a true MMN rather than a frequency-specific negativity following the presentation of the deviant. First, it occurred in the expected MMN latency range (100-150 ms in this case). Second, it was maximal at fronto-central sites thus conforming to the scalp distribution of the MMN reported in the literature (Näätänen & Michie, 1979; Giard et al., 1990). Finally, this negative wave reversed in polarity (positive-going deflection) at the mastoid electrode. It has been shown that the MMN will invert at the mastoid when a nose reference is used (Alho et al., 1986).

Deviant auditory stimuli may however elicit a variety of negative components in the auditory ERP during sleep. In wakefulness, the N1 (peaking at approximately 100 ms) wave is enhanced by rare deviant stimuli, relative to frequent standards. While the amplitude of the N1 has been shown to decline to near baseline levels during NREM sleep, a small N1 may "re-appear" in REM sleep (Campbell et al., 1992). In NREM sleep, repetitive stimuli presented at long intervals may elicit a negative wave at approximately 350 ms (N350), often labelled as the "sleep N2" (Näätänen & Picton, 1987). The N350 may be related to the N2 wave seen in wakefulness but the former is larger in amplitude and has a longer peak latency (Nielsen-Bohlman et al., 1991). In REM sleep, N350 amplitude may be close to levels seen for the waking N2 (Weitzman & Kremen, 1965; Campbell et al., 1992).

The contention that a MMN is present in REM sleep would be further strengthened by demonstrating that the observed deviant-related negative wave is not due to other sources. This may be accomplished by employing a stimulus condition involving changes in the duration of a tone. The duration-deviance manipulation allows for the dissociation of the MMN from other negativities that might be "time-locked" to the occurrence of the deviant stimulus *alone*. For example, a 50 ms deviant will elicit a MMN that peaks later when it is paired with a 100 ms standard than when it is presented with a 25 ms standard. In the former case, the response to the deviant would not be initiated until 50 ms had elapsed, whereas in the latter case the deviant would be initiated after only 25 ms.

Näätänen et al. (1989) demonstrated that the peak latency of the MMN could be "shifted" in time by manipulating the duration of the deviant while keeping the duration of the standard constant. They used a series of conditions in which the duration of the deviant was either twice that of the standard (duration increment) or one-half that of the standard (duration decrement). A MMN was elicited by both deviant increments and decrements, but its peak latency increased as the duration of the tones increased. In contrast, the peak latency of N1 remained constant. In a separate condition, they presented the brief deviants alone without the intervening standards. In this case, a large N1 response was elicited but no MMN was observed. This demonstrated that the elicitation of the MMN was dependent upon the existence of a temporal contingency between the deviant and a standard exemplar.

The existence of a genuine MMN process can be further established by implementing a duration-decrement condition. This allows for the dissociation of the MMN from the negative sustained potential (Picton et al., 1978) which is elicited by longer duration stimuli.

If a deviant-related negative component is elicited by a short duration deviant but not by the longer duration standard, then the sustained potential can be excluded as a possible source of the negativity. In the present study, two stimulus conditions, involving either duration-increment or duration-decrement deviant stimuli were presented during various sleep stages.

There are no reports in the literature concerning the MMN to auditory stimulus duration deviance during sleep in humans. It is expected however that the sleep-specific N350 component is more likely to be elicited by the increment deviants. Stimuli that are more "intrusive" (Bastien & Campbell, 1992) elicit a larger N350 response. A greater negativity in this latency range may therefore be associated with the increment deviants.

Methods

Subjects

Eight young adults (5 females & 3 males; aged 22-27; mean=23.3 years) spent a single night in the sleep laboratory. All subjects were self-reported good sleepers with no reported history of psychiatric or neurological disorder. Subjects were tested for normal hearing (15 dB ISO) at 500, 1000, 2000 and 4000 Hz. They were instructed to refrain from alcohol and caffeine intake during the 24 hour period prior to recording. Informed, written consent was obtained prior to the study and a small honorarium was offered as compensation.

Procedure

Subjects were presented with two different "oddball" stimulus conditions in which the

duration of tone pips was manipulated. In the Increment condition, 150 ms deviants were presented among a series of 100 ms standards. In the Decrement condition, 50 ms deviants were presented among 100 ms standards. Stimuli within each condition were presented in blocks consisting of 500 trials. The probability was .90 for the standards and .10 for the deviants. The probability of deviant occurrence was reduced in this study compared to the frequency MMN study. The reason was to maximize the amplitude of the MMN, especially in NREM. The MMN increases in amplitude with decreasing deviant probability (Näätänen, 1992). All stimuli were 1000 Hz tones presented at 80 dB SPL with a rise-and-fall time of 5 ms. The inter-stimulus interval (ISI) was a constant 0.6 ms. Deviants occurred randomly within the block but were separated by at least one standard tone.

Auditory stimuli were transduced by a custom designed hearing-aid device containing a Knowles ED-197 wide bandbass speaker. The output of the speaker was conducted through standard no. 13 tubing (1.93 mm in diameter) attached to an individually fitted ear mould placed in the left ear of the subject. The tightly fitting hearing-aid device assured constancy of stimulus input to the ear of the subject in spite of movements by the subject during the overnight sleep recording. The auditory output was calibrated using a Bruel and Kjaer 2209 sound level meter and a 2 cm^3 acoustic coupler.

Recordings were conducted in an acoustically shielded sleep chamber. Stimuli were presented during wakefulness as subjects read a book (thus ignoring the stimuli) and also during the subsequent night's sleep. The two stimulus conditions were presented during electrographically-determined sleep stages 2, 4 and REM (as defined by the criteria of Rechtschaffen and Kales, 1968). Stage 2 sleep was subdivided into "early" and "late" halves

to examine possible time-of-night differences. In cases of sleep stage ambiguity, data were excluded from analysis. In addition, trials associated with stage changes or subject movements and arousals were also excluded. An attempt was made to obtain three repetitions of the stimulus conditions from each stage of sleep. Due to time constraints, complete blocks were not always collected. Late Stage 2 and SWS data were not obtained from one subject because of the short length of time spent in these stages by this individual.

Physiological Recording

EEG and EOG were recorded using Grass gold electrodes attached to the scalp with collodion-soaked gauze. EEG electrodes were placed at midline frontal, central, and parietal (Fz, Cz, Pz) sites. Additional electrodes were placed at three equidistant lateral sites located on a line extending from Fz to the right mastoid. These were labelled R1, R2, and R3. These sites were chosen because the MMN to duration deviants has been shown to be larger over the right hemisphere (Giard et al., 1991; Paavilainen et al., 1991). All EEG sites were referenced to an electrode placed on the tip of the nose. When a nose reference is used a true MMN shows a polarity reversal at the mastoid (R3) site (Alho et al., 1986).

The EOG was recorded from an electrode placed one centimetre above the outer canthus of one eye referenced to another electrode placed one centimetre below the outer canthus of the other eye. This permitted the recording of both vertical and horizontal eye movements on a single channel. The EEG and EOG were recorded with a high frequency setting of 35 Hz and a time constant of 2.0 s. Inter-electrode impedance was below 5 kOhms. The EEG and EOG were also collected on paper at a speed of 10 mm/s for

purposes of sleep staging.

The EEG and EOG were stored continuously to disk at a rate of 512 Hz. Discrete epochs (trials) were constructed off-line. Each sweep consisted of 256 data points beginning 50 ms prior to stimulus onset and continuing for 462 ms following it. For the waking data, trials in which the EEG or EOG exceeded $\pm$ 100 μV were rejected from the average. For the sleep data, the artifact rejection was set at $\pm$ 150 μV, allowing most delta activity to pass but rejecting high amplitude frontal K-Complexes which characterize NREM sleep and eye movement artifact (horizontal or vertical rapid eye movements) seen in REM sleep. The standard and deviant average waveforms for each condition were digitally filtered using a bandwidth of 3.0 to 30 Hz (3 dB roll-off). The low frequency filter setting selected was unusually high. The 3.0 Hz low frequency cut-off served as a compromise to attenuate the effects of large amplitude slow waves in NREM without affecting the slow frequency component of the MMN (see Loewy et al., Appendix A).

Statistical Analysis

The MMN is best observed in a "difference wave", which is calculated by subtracting, point by point, the average of the standard presentations from each of the deviant averages. The difference waves were then subdivided into nine 50 ms intervals starting at stimulus onset. Within each of these intervals, the average of all data points was computed, yielding an average amplitude measure. A similar method for scoring the MMN has been used by Näätänen and his colleagues (see for example, Alho et al., 1986; and Alho et al., 1989).

The problem of determining the presence of the MMN in sleep has been discussed by Loewy et al. (in press). In brief, one approach would be to compare waking and sleeping ERPs. The failure to find a difference cannot however be used to imply the presence of a MMN in sleep. Similarly, a difference between the waking and sleeping waveforms cannot imply the absence of a MMN. For this reason, confidence intervals were computed for each of the nine latency intervals to determine if a MMN could be recorded in each stage of sleep. This procedure determined whether the probability of the mean value of an particular interval fell within an upper or lower range. If the lower limit was significantly less than the 0 μV baseline (i.e., was negative), the interval was considered to contain an MMN. A one-tailed test of significance was used ($p < .05$) because a negative directionality was predicted (i.e., the polarity of the MMN should be negative). To restrict the likelihood of a chance finding, the latency and scalp distribution had to correspond to that reported in the literature. Thus it had to occur in the 100-300 ms latency range and have a fronto-central maximum amplitude. As well, the amplitude had to show a decline at posterio-lateral sites and reverse in polarity at the mastoid location (R3).

Results

Increment Deviance

The grand average waveforms to the 100 ms standard and 150 ms deviant tones are presented in Figure 3.1. When subjects were awake and reading, both standards and deviants elicited a small amplitude N1-P2 complex. The amplitudes of the N1-P2 waves

were similar for both types of stimuli, peaking at approximately 110 and 170 ms respectively at Cz. In addition, a late positive centro-frontal wave, following the deviant, was evident at approximately 340 ms. The difference waveforms (deviant minus standard) appear in the lower portion of the figure. The waking difference wave revealed a large negative wave associated with the deviant tones. This negativity was significantly above baseline ($p < .05$) at frontal and central sites throughout the 150-200, 200-250, and 250-300 ms intervals. Inspection of Figure 3.1 indicates that this negativity reversed polarity (positivity) at the mastoid location (R3) in the 150-250 ms range, but not in the 250-300 ms intervals. The mean amplitudes of the difference waves for Fz, Cz and R3 electrode sites are presented for each interval in Table 3.1. Based on its 150-300 ms latency, its fronto-central distribution, and its inversion a the mastoid, this negativity probably represents a true MMN.

During early Stage 2 sleep, the deviant stimuli appeared to elicit a prominent N1-like wave at approximately 140 ms. Only a very small frontal N1 was elicited by the standards. A small P2 was seen at 210 ms for deviants but no discernable P2 was apparent for the standards. The difference wave revealed three significant negative peaks in the 100-150, 250-300, and 400-450 ms intervals, but they all had a parietal maximum (see Table 3.2). This first peak had a centro-parietal maximum amplitude and appeared to correspond to the enhanced negativity in the N1 latency range for deviants. The second peak occurred in latency range for the MMN but it had a centro-parietal maximum and did not invert in polarity at the mastoid. The third negative peak was also had a centro-parietal maximum and did not show the mastoid inversion. In late Stage 2 sleep, N1 and P2 were close to baseline for both standards and deviants. The difference wave revealed no significant negativity in

the MMN latency range. A late but non-significant negative peak was evident at the Cz electrode in the 350-400 ms interval.

In SWS, the grand average waveforms showed a late negative-positive complex for deviants, peaking at approximately 190 and 250 ms, respectively. The difference wave revealed a large significant ($p < .05$) negativity in the 150-200 ms latency interval (see Table 3.2). This negativity was evenly distributed along the midline but did reveal a trend toward the mastoid polarity inversion. A late centro-parietal positivity was observed at approximately 420 ms.

For REM sleep, the standard and deviant grand average waves both showed N1 to be reduced to near baseline for both deviants and standards. A late central positivity could be seen for deviants at 400 ms, but it was smaller in amplitude and had a longer latency than that seen in wakefulness. The difference wave revealed a much attenuated negativity in the 200-250 ms interval. This negativity did not attain significance, although it did invert in polarity at the mastoid. A second late small amplitude negativity appeared at 300 ms, but it also failed to attain statistical significance, and moreover it did not show the mastoid inversion. The mean amplitudes within each interval for REM appear in Table 3.1.

---------- Insert FIGURE 3.1 and TABLES 3.1 & 3.2 About Here ----------

Decrement Deviance

The grand average waveforms to the 100 ms standard and 50 ms deviant tones are presented in Figure 3.2. During wakefulness, a small N1-P2 complex was evident at 110

and 170 ms respectively. A late positivity appeared in the deviant waveform at approximately 310 ms. The difference waves appear in the lower portion of the figure. A 150-250 ms negativity, with a fronto-central maximum amplitude, was evident in the awake difference. This negativity was significantly ($p < .05$) above baseline during the 150-200 and 200-250 ms intervals. It reversed in polarity at the mastoid within these intervals. The latency, scalp distribution and mastoid inversion of this negativity are consistent with the characteristics of the MMN. The mean amplitudes of the difference waves for Fz, Cz and R3 are presented for each interval in Table 3.3.

In early Stage 2, the difference wave revealed two vertex maximal negativities in the 150-200 and 300-350 ms intervals. The early negativity was not considered to be a MMN since it tended to be larger at Pz than Fz and a polarity reversal at the mastoid was not distinct. None of the amplitudes at any interval were statistically significant. In late Stage 2, the difference wave revealed a single negativity in the 150-200 ms interval but it was not significant and again did not show an inversion at the mastoid. The mean amplitudes for early Stage 2 and late Stage 2 appear in Table 3.4.

The grand average ERPs to the deviants remained noisy during SWS. In the difference wave, a single negativity was evident within the 150-200 ms interval but this was non-significant (see Table 3.4). There was a very small inversion at the mastoid. This negativity was followed by a large amplitude parieto-central positivity peaking at approximately 400 ms.

During REM sleep, N1 was close to baseline but P2 remained visible, peaking at approximately 200 ms for both standards and deviants. A small frontal negativity that

inverted in polarity at the mastoid was evident in the 150-200 ms interval (see Table 3.3). Again, neither it nor any of the other intervals were significantly above baseline. The late but small positivity seen for the increment deviants was somewhat earlier (350 ms) for the decrements, but it was not significantly different from baseline.

---------- Insert FIGURE 3.2 and TABLES 3.3 & 3.4 About Here ----------

Increment and Decrement Deviants

The difference waves for the increment and decrement deviants for each wake/sleep condition are superimposed in Figure 3.3. This representation allows for the examination of the temporal shift in peak latency between the MMNs associated with the long 150 ms and short 50 ms duration deviants (standard=100 ms). In wakefulness, it can be seen that the amplitude of the MMNs to the two deviants were similar. The increment MMN had a greater parietal contribution than did the decrement MMN. This is indicated by statistical significance of the negativity, relative to baseline, in the 250-300 ms interval for increments (see Table 3.1). The decrement MMN peaked approximately 50 ms earlier than the increment MMN. The peak of the decrement MMN occurred at approximately 225 ms and the peak of the increment MMN occurred at approximately 275 ms.

The temporal relationship between the deviant negative peaks seen in wakefulness was not apparent in any of the NREM stages. There was some evidence however of a temporal displacement of deviant-related negativities in REM sleep. During REM sleep, a very small fronto-central negativity was apparent in the 220-250 ms interval and a larger central

negativity in the 250-300 ms interval for the increment deviant. For the decrement deviant, a small frontal negativity was evident in the 150-200 ms interval. The respective latencies of these negativities showed a strong correspondence to the latencies of the MMNs seen in the waking condition for increments (150-300 ms) and decrements (150-200 ms).

---------- Insert FIGURE 3.3 About Here----------

Discussion

When subjects were awake and reading, the 150 ms duration-increment deviants elicited a long-lasting fronto-central MMN during the 150 to 300 ms post-stimulus period. The 50 ms duration-decrement deviants elicited a fronto-central MMN at approximately 150-250 ms. The amplitudes of the two MMNs were very similar. The earlier onset of the MMN to deviant decrements is consistent with previous findings (Näätänen et al., 1989). Detection of the decrement can begin after the offset of the deviant (i.e., after 50 ms) while the detection of the increment cannot begin until the offset of the standard (i.e., after 100 ms). The temporal shift in the onset of the MMN corresponds to this 50 ms delay.

It is, of course, possible that the negative difference elicited by the deviant increment is not a MMN. Rather, it may be a reflection of a negative sustained potential (Picton et al., 1978), the negativity being "sustained" by the presence of the stimulus. The sustained potential would last longer for the deviant increment than the standard since its duration is longer. On the other hand, such an argument cannot be used to explain the enhanced

negativity following the deviant decrement. The sustained potential should have lasted longer for the standard than the short deviant. As such, the difference wave would have revealed a positivity rather than the negativity that was observed.

The fronto-central distribution of both the increment and decrement deviants is consistent with the scalp distribution of the MMN reported elsewhere (Näätänen & Michie, 1979; Giard et al., 1990). In addition, the early portion of the negativity showed polarity inversion at the mastoid. It has been shown that the MMN will invert at the mastoid when a nose reference is used (Alho et al., 1986). An additional negativity appeared to be superimposed on the later 250-300 ms portion of the MMN. This was apparent for both increments and decrements. This late negativity did not however invert at the mastoid. This negativity may represent a superimposition of N2b. N2b can be distinguished from the MMN by its failure to invert at the mastoid (Näätänen et al., 1989)

The possible presence of an N2b suggests that even while subject were engaged in the distracting task (reading a book), the deviants may have "intruded" into conscious awareness. This is supported by the appearance of a late positivity, possible reflecting the P3a which may also occur in "ignore" conditions for intrusively deviant stimuli (Sams et al., 1985). The P3a is distinguishable from the P300 (or P3b) by a more anterior scalp distribution.

In Stage 2 sleep, the difference wave for the deviant increments showed three significant negative waves. The first two occurred in the typical MMN latency range (100-300 ms). They did not however show the scalp distribution indicative of the MMN. They were prominent parieto-centrally and did not show polarity inversion at the mastoid. The third negative wave occurred at 400-450 ms, well beyond the latency range expected for the

MMN. The decrement deviants elicited two smaller negative waves in the MMN latency range. These were also maximal parieto-centrally and were not significant. In slow wave sleep, a significant negative wave was elicited by the increment deviants at 150-200 ms, but it did not show the typical MMN scalp distribution. A small amplitude but non-significant negative wave was elicited by the decrement deviants in the same latency range but it too failed to conform to the MMN scalp representation.

The absence of a MMN in SWS is consistent with the findings of Loewy et al. (in press) who failed to observe a MMN to frequency changes in SWS. The deviant waveforms in both Stage 2 and SWS were quite noisy. If a true MMN, of small amplitude, was elicited, it would be difficult to distinguish it in the background noise. The deviant probability was lowered to .10 in this study compared to the .20 deviant probability used for frequency deviants by Loewy et al. (in press). While this may increase the amplitude of the MMN, fewer trials were available for averaging. As a result, the amplitude of the background EEG may have remained quite high following averaging.

In late Stage 2, a large late fronto-central negative peak was evident at 350-400 ms for deviant increments and a smaller parieto-central peak was evident at 150-200 ms for decrement deviants. Other researchers have reported late negative waves, between 350-500 ms, associated with deviant auditory stimuli in sleep. These studies have however only examined deviations in pitch (Nielsen-Bohlman et al., 1991; Salisbury & Squires, 1992; Harsh et al., 1994; Winter et al., 1995). The functional role of the late negativities is not known. A late N350 wave may form part of a very large and still later K-Complex or it may occur independently of the K-Complex (Bastien & Campbell, 1992; Salisbury &

Squires, 1993).

In REM sleep, a small amplitude negativity was elicited in the 200-250 ms and 250-300 ms intervals for increment deviants, and in the 150-200 ms interval for decrement deviants. The early 150-250 ms negative waves were larger frontally, while the later 250-300 ms negativity for deviant increments was larger at the vertex. In addition, the negativities became smaller at posterio-lateral sites and reversed polarity at the mastoid site. Moreover, the early latency shift between decrement and increment deviants that occurred in the waking state was replicated during REM. The negativities observed in REM thus met the criteria for the MMN. However, neither wave was significantly above baseline (negative) when the nose reference was used.

The displacement of the negativity between increments and decrements discounts the argument that the small amplitude negativity for increment deviants was due to the appearance of a small N1 wave. The MMN may overlap N1, especially for widely deviant stimuli presented at rapid rates (Näätänen & Picton, 1987). While N1 is strongly attenuated in NREM sleep (Paavilainen et al., 1987; Nielsen-Bohlman et al., 1991), a small amplitude N1 may "re-appear" in REM sleep (Campbell et al., 1992). The peak latency of the N1 would however remain constant for both increment and decrement deviants and thus could not account for the temporal shift of the negativity in REM.

It would thus appear that if the MMN to duration deviants can be elicited following the onset of sleep, it will be during REM but not during NREM sleep. This is consistent with previous findings from our lab of a small amplitude MMN in REM sleep for frequency deviations (Loewy et al., in press). Studies of awake and alert subjects indicate that the

frequency MMN is much less affected by manipulation of selective attention than the intensity MMN (Woldorff et al., 1991; Näätänen et al., 1993). Unfortunately, little is known about the effects of conscious awareness of the duration MMN. It is possible that, like the MMN for intensity deviance, the MMN to stimulus duration changes is also more attenuated in REM than the frequency MMN.

		1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
AWAKE	**Fz**	-0.38 (0.63)	-0.21 (1.13)	-0.54 (1.48)	-1.06* (1.02)	-1.85* (1.12)	-1.51* (1.19)	0.28 (1.12)	0.38 (1.13)	-0.29 (0.51)
	Cz	-0.06 (0.82)	-0.21 (1.35)	-0.38 (1.42)	-0.83* (0.85)	-1.87* (1.26)	-1.94* (1.35)	1.14 (2.05)	0.98 (1.62)	-0.21 (0.71)
	R3	-0.15 (0.42)	-0.19 (0.70)	0.03 (0.55)	0.70 (0.53)	1.28 (0.66)	0.97 (0.70)	0.68 (1.34)	1.55 (1.31)	1.16 (0.65)
REM	**Fz**	0.27 (0.69)	0.36 (0.95)	0.57 (1.17)	0.19 (1.34)	0.55 (0.99)	-0.08 (0.86)	0.02 (1.04)	0.86 (1.29)	0.57 (1.06)
	Cz	0.38 (0.73)	0.42 (0.93)	0.53 (1.33)	0.23 (1.22)	0.23 (0.96)	-0.17 (0.85)	-0.19 (1.39)	0.59 (1.42)	0.50 (1.07)
	R3	0.02 (0.29)	0.41 (0.76)	0.53 (0.59)	0.86 (0.57)	0.93 (0.93)	0.99 (0.88)	0.83 (0.96)	0.59 (1.09)	0.50 (0.72)

Table 3.1

Increment deviance: Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 450 ms sweep (n=8). * denotes negative amplitude values that were significantly different from baseline ($p < .05$).

		1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
STAGE 2 Early	**Fz**	-0.38 (0.90)	-0.97* (1.03)	-1.83* (1.22)	-1.98* (2.35)	-1.91 (2.82)	-2.20 (3.21)	-1.67 (4.21)	-1.43 (4.55)	-0.76 (2.91)
	Cz	-0.71 (1.08)	-1.43 (2.45)	-2.51* (1.67)	-2.09* (2.32)	-2.42 (3.55)	-2.73 (3.34)	-2.13 (3.88)	-2.71 (4.53)	-1.70 (2.79)
	R3	-0.17 (0.60)	-0.35 (1.12)	-0.44 (1.01)	-0.10 (1.11)	-0.44 (1.08)	-0.56 (0.97)	-0.74* (0.81)	-1.00* (0.72)	-0.52* (0.47)
SWS	**Fz**	-1.03 (1.93)	-1.48 (3.59)	-1.72 (3.63)	-3.37* (2.47)	-3.16 (3.75)	-2.61 (6.41)	-2.40 (6.96)	-1.18 (6.84)	-0.33 (4.85)
	Cz	-0.58 (3.63)	-0.53 (7.71)	-0.78 (8.06)	-3.08 (4.88)	-3.45 (3.88)	-2.95 (6.40)	-2.25 (7.07)	-0.18 (7.10)	0.46 (4.79)
	R3	-0.79 (1.56)	-1.49 (2.96)	-1.58 (3.51)	-1.50 (4.23)	-2.09 (4.45)	-2.42 (4.86)	-2.24 (4.95)	-1.66 (5.62)	-0.63 (3.82)
STAGE 2 Late	**Fz**	-0.19 (0.84)	0.20 (1.25)	0.73 (1.58)	0.35 (1.99)	0.55 (2.75)	0.29 (4.22)	0.24 (3.75)	-0.70 (4.24)	-0.24 (2.74)
	Cz	0.06 (1.28)	0.09 (1.42)	0.28 (1.79)	0.28 (2.13)	0.03 (2.91)	-0.21 (4.52)	-0.50 (4.10)	-1.34 (4.23)	-0.27 (2.42)
	R3	0.05 (0.33)	0.22 (0.86)	0.05 (1.24)	0.04 (1.50)	-0.20 (1.69)	-0.32 (2.01)	-0.25 (1.90)	0.05 (1.85)	0.26 (1.08)

Table 3.2

Increment deviance: Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 450 ms sweep. For Stage 2 - Early, n=8. For SWS and Stage 2 - Late, n=7. * denotes negative amplitude values that were significantly different from baseline ($p < .05$).

		1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
AWAKE	**Fz**	-0.08 (0.69)	-0.48 (1.09)	-0.70 (1.36)	-1.75* (0.76)	-1.89* (1.03)	-0.63 (1.12)	-0.03 (2.22)	-0.71 (2.21)	-0.68 (1.16)
	Cz	0.06 (0.60)	-0.24 (0.61)	-0.41 (0.88)	-1.03 (0.55)	-2.00* (1.04)	-0.29 (1.10)	0.42 (2.71)	-0.85 (2.15)	-0.56 (1.10)
	R3	-0.01 (0.43)	-0.13 (0.32)	-0.13 (0.49)	1.02 (0.83)	0.82 (1.12)	-0.17 (1.13)	0.40 (1.20)	0.92 (1.43)	0.42 (1.23)
REM	**Fz**	-0.07 (0.38)	-0.09 (0.81)	-0.23 (0.70)	-0.57 (1.15)	-0.42 (1.94)	-0.22 (1.46)	-0.08 (1.36)	-0.13 (1.55)	-0.39 (1.09)
	Cz	0.11 (0.50)	-0.11 (0.92)	-0.39 (0.89)	-0.32 (1.63)	-0.42 (2.12)	-0.18 (1.63)	0.31 (1.69)	-0.07 (2.18)	-0.51 (1.55)
	R3	-0.02 (0.36)	-0.19 (0.69)	-0.08 (0.84)	0.07 (1.11)	-0.16 (1.14)	-0.16 (1.06)	0.08 (1.09)	0.09 (1.03)	0.07 (0.61)

Table 3.3

Decrement deviance: Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 450 ms sweep (n=8). * denotes negative amplitude values that were significantly different from baseline ($p < .05$).

		1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
STAGE 2 Early	**Fz**	0.36 (1.07)	0.61 (1.91)	0.88 (2.39)	0.69 (2.39)	0.91 (2.02)	0.86 (1.76)	-0.01 (2.31)	0.18 (3.54)	0.62 (2.29)
	Cz	0.44 (1.42)	0.58 (2.32)	0.69 (3.01)	0.09 (3.36)	0.94 (2.79)	0.66 (2.24)	-0.26 (2.30)	-0.17 (3.52)	0.38 (2.39)
	R3	-0.19 (0.45)	-0.28* (0.29)	-0.32 (0.86)	-0.18 (1.17)	-0.32 (1.40)	-0.52 (1.60)	-0.65 (1.87)	-0.82 (2.22)	-0.74 (1.37)
SWS	**Fz**	0.16 (2.20)	1.07 (3.83)	1.68 (4.66)	0.92 (4.45)	0.39 (4.82)	1.33 (4.97)	2.17 (4.30)	1.62 (4.89)	0.31 (3.30)
	Cz	0.73 (2.74)	1.55 (3.93)	1.65 (4.37)	0.67 (5.40)	0.47 (4.65)	1.67 (3.75)	2.45 (4.68)	2.65 (6.30)	1.57 (3.98)
	R3	0.33 (0.68)	0.43 (1.21)	-0.06 (1.69)	0.11 (1.89)	-0.07 (2.18)	0.05 (2.63)	0.01 (2.35)	0.16 (2.93)	0.58 (2.15)
STAGE 2 Late	**Fz**	0.08 (0.64)	0.05 (1.17)	0.58 (1.77)	0.57 (2.35)	0.94 (3.28)	1.06 (3.71)	0.30 (3.12)	-0.24 (2.72)	-0.53 (1.60)
	Cz	0.38 (0.99)	0.34 (1.52)	0.81 (2.02)	0.74 (0.74)	1.26 (3.35)	1.35 (4.02)	0.67 (3.50)	-0.16 (3.63)	-0.63 (2.54)
	R3	-0.01 (0.37)	0.03 (0.55)	-0.11 (0.83)	-0.17 (0.82)	-0.21 (0.53)	-0.19 (0.56)	-0.27 (0.81)	-0.45 (1.28)	-0.36 (0.95)

Table 3.4

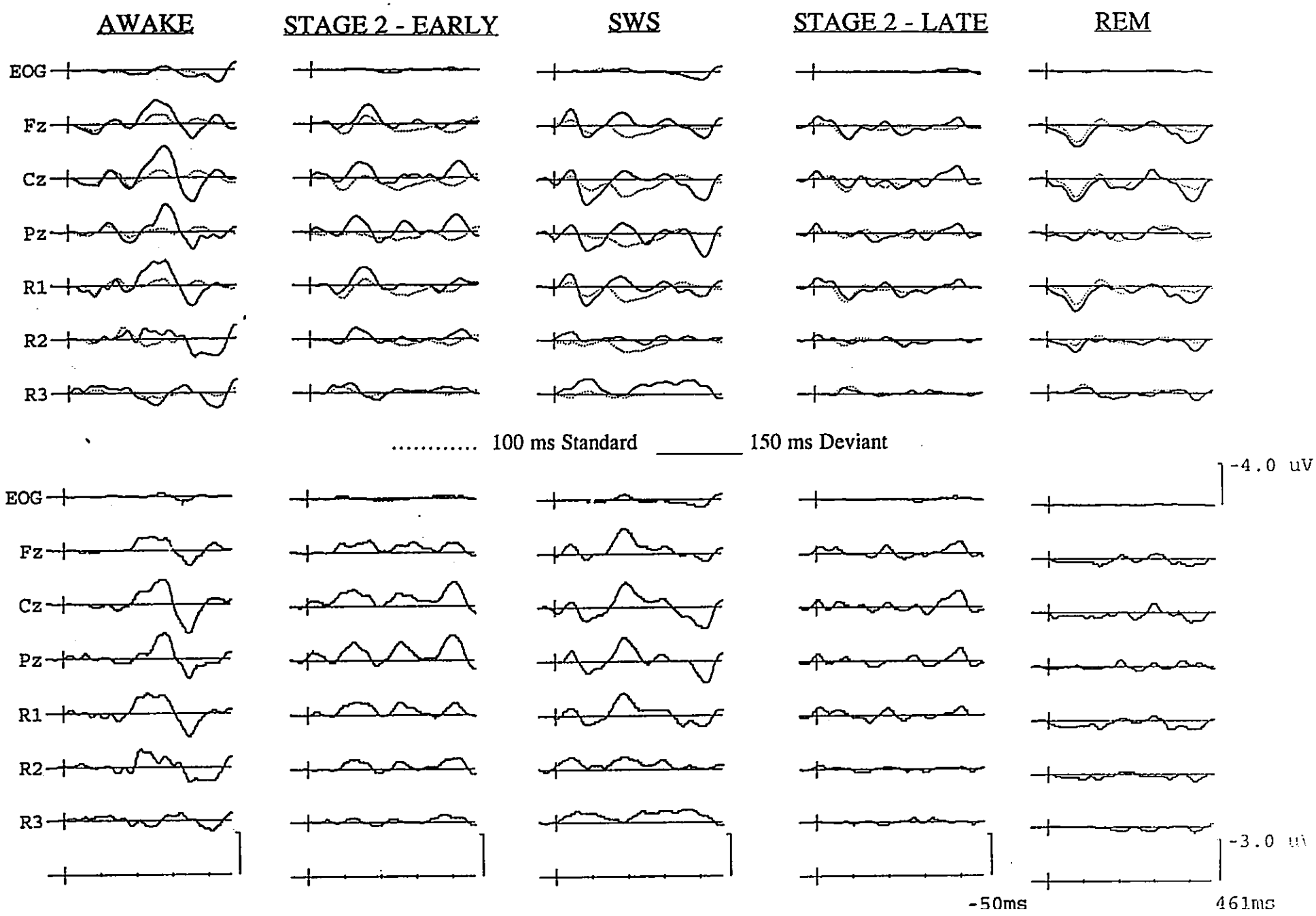
Decrement deviance: Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 450 ms sweep. For Stage 2 - Early, n=8. For SWS and Stage 2 - Late, n=7. * denotes negative amplitude values that were significantly different from baseline ($p < .05$).

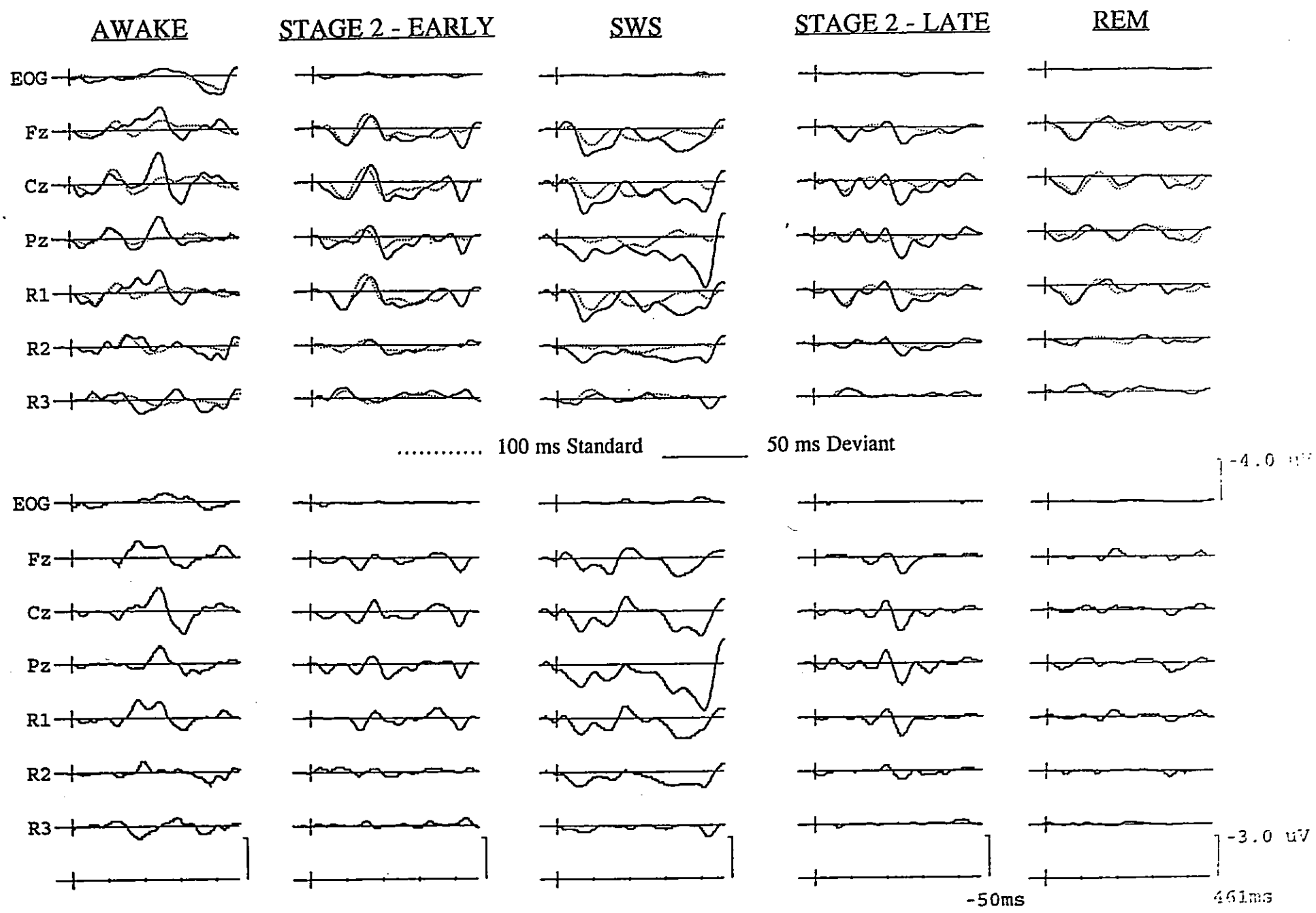
Figure Legend

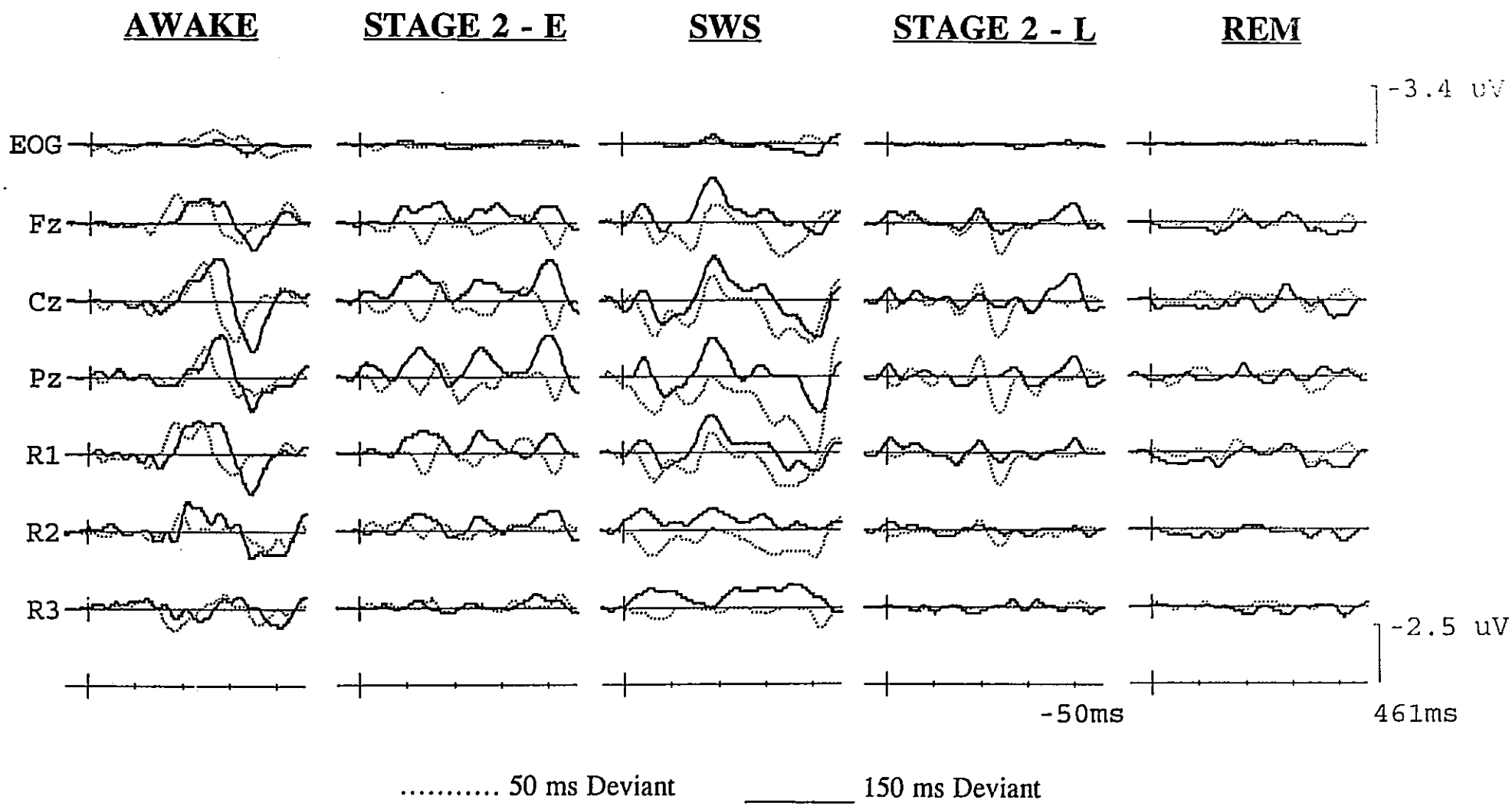
Figure 3.1. Increment deviant (150 ms) and standard (100 ms) grand average waveforms for Awake, early Stage 2, late Stage 2, Stage 4, and REM. Deviant-standard difference waveforms appear in the lower portion.

Figure 3.2. Decrement deviant (50 ms) and standard (100 ms) grand average waveforms for Awake, early Stage 2, late Stage 2, Stage 4, and REM. Deviant-standard difference waveforms appear in the lower portion.

Figure 3.3. Difference waves (deviant - standard) for Awake, early Stage 2, late Stage 2, Stage 4, and REM for increment (150 ms) and decrement (50 ms) deviant conditions.


AWAKE
STAGE 2 - EARLY
SWS
STAGE 2 - LATE
REM
EOG
Fz
Cz
Pz
R1
R2
R3
..... 100 ms Standard _____ 150 ms Deviant
-4.0 uV
-3.0 uV
-50ms
461ms


AWAKE
STAGE 2 - EARLY
SWS
STAGE 2 - LATE
REM
EOG
Fz
Cz
Pz
R1
R2
R3
..... 100 ms Standard
50 ms Deviant
-4.0 uV
-3.0 uV
-50ms
461ms


AWAKE
STAGE 2 - E
SWS
STAGE 2 - L
REM
-3.4 uV
EOG
Fz
Cz
Pz
R1
R2
R3
-2.5 uV
-50ms
461ms
..... 50 ms Deviant
_____ 150 ms Deviant

Chapter 4

Experiment III: The Mismatch Negativity During Natural Sleep: Intensity Deviants

This study is currently "in preparation" for submission to the journal *Electroencephalography and Clinical Neurophysiology*. Auditory stimuli deviating in intensity were presented during a waking reading condition, Stage 2, and REM sleep. Recordings were not made during SWS because results from the two previous studies provided no indication of the presence of a MMN in this stage. In a single stimulus condition, infrequent 80 dB "increment" and 60 dB "decrement" deviant tones were presented with frequently occurring 70 dB standards. The results from experiment 1 (Chapter 2) indicated that a MMN to frequency change could be elicited in REM sleep. The results concerning the MMN to duration change in Experiment 2 (Chapter 3) were less clear. The duration MMN may be more susceptible to loss of attention in the form of natural sleep than the frequency MMN. The waking selective-attention literature indicates that the MMN to intensity change is highly influenced by attentional withdrawal. Therefore the intensity MMN will probably be greatly attenuated in sleep.

Introduction

When a subject is presented with a deviant auditory stimulus occurring in a homogeneous sequence of background "standard" stimuli, a "mismatch negativity" (MMN) is elicited (Näätänen et al., 1978). The MMN is a negative event-related potential (ERP) wave that typically begins about 100 ms and lasts up to 300 ms after stimulus onset. It has been shown that the MMN can be elicited by a variety of auditory stimulus changes including pitch (Näätänen et al., 1978; Sams, Paavilainen et al., 1985), intensity (Näätänen et al., 1987; Näätänen et al., 1993), duration (Näätänen et al., 1989; Novak et al., 1992), inter-stimulus interval (Böttcher-Gandor, 1992; Ford & Hillyard, 1981; Nordby et al., 1988), spatial location (Paavilainen et al., 1989), complex phonetic changes (Aaltonen et al., 1987; Sams et al., 1990), and stimulus omissions (Nordby et al., 1994). The amplitude of the MMN increases and the peak latency decreases as the magnitude of difference between the deviant and standard increases (Sams et al., 1985; Paavilainen et al., 1989). The MMN is also larger when a short inter-stimulus interval (ISI) is used and deviant probability within the sequence is low (Näätänen & Mantysalo, 1987; see review by Näätänen, 1992).

The MMN is often recorded in experimental conditions in which the subjects are engaged in a secondary task, such as reading a book, and thus ignoring the stimuli. This is based on the assumption that the MMN is unaffected by the subject's level of attention or conscious awareness of the deviant stimulus. This assumption seems to be reasonably well supported when frequency deviants are employed. In selective-attention tasks, when attention is focused on a specific channel, the MMN elicited by frequency deviants does not appear to

be markedly altered by the direction of attention (Alho et al. 1989; Näätänen et al., 1978; Sams, Paavilainen et al., 1985). The MMN to frequency deviants can also be recorded during states of unconsciousness. Previous studies in our laboratory (Campbell et al., 1992; Loewy et al., in press) have indicated that the MMN following frequency deviants can also be recorded in REM sleep, but not during NREM sleep. Sallinen et al. (1994) however reported the elicitation of a frequency MMN in Stage 2 sleep when the deviant stimulus was associated with the elicitation of a K-Complex, but not when no K-Complex was present. Similarly, Kane et al. (1993) recorded frequency-elicited MMN in certain comatose patients such that the presence of the MMN was shown to predict recovery. Patients, for whom the MMN could be recorded, regained consciousness within two to three days.

The hypothesized attentional independence of the MMN has been challenged recently by findings concerning the MMN elicited by stimuli deviating in intensity. Previous studies had shown that the MMN could be elicited during "ignore" conditions by occasional intensity increments or decrements (Snyder & Hillyard, 1976; Näätänen et al., 1978; Näätänen et al., 1987; Näätänen et al., 1989; Winkler et al., 1990; Paavilainen et al., 1991). In a selective-attention condition, Alho et al. (1989) presented small intensity decrements (60 dB vs. 75 dB standards) in a dichotic-listening paradigm. The ISI used was 410 ms and deviants occurred with a probability of either .05 or .10. They reported equivalent MMNs for identical deviants whether they were presented in an attended or unattended channel. In contrast, Woldorff et al. (1991) used intensity decrements in a more difficult selective-attention task. Slight deviant decrements (35-45 dB vs. 55 dB standards) were presented at a very low probability (.09) and at very rapid rates (ISI = 120-320 ms). They observed a smaller

amplitude MMN to non-attended intensity deviants. The authors attributed this finding to an attenuation of the MMN for the unattended deviants due to the strong focusing of attention toward the attended deviants. Näätänen et al. (1993) recorded MMNs to frequency and intensity changes during tasks requiring a strong attentional focus. The MMNs to the frequency deviants were unaltered by attention. In contrast, intensity decrements (70 dB deviant, 80 dB standard), occurring in a non-attended channel, elicited a smaller amplitude MMN than the same stimuli presented to an attended channel.

Although some laboratories have presented stimuli deviating in frequency during states of unconsciousness, none have presented intensity deviants. The purpose of this study was to evaluate the sensitivity of the intensity MMN to attention by recording ERPs to intensity auditory changes during sleep. In previous studies, we have found no indication of MMN-like negativities present during slow wave sleep (SWS, Stages 3 & 4) for either frequency (Campbell et al., 1992; Loewy et al., in press) or duration (Loewy et al., in preparation) changes. Other researchers (Paavilainen et al., 1989; Nielsen-Bohlman et al., 1991) have similarly been unable to record the MMN in SWS. In the present study therefore, ERPs are recorded only during REM and Stage 2 sleep. An intensity increment and decrement condition were used and stimuli were presented at a rapid rate. The use of an intensity decrement condition was intended to overcome the problem of an enhancement of N1, which may overlap in the MMN latency range. N1 amplitude may greater for intensity increments due to activation of "fresh" neural elements associated with processing louder stimuli (Näätänen & Picton, 1987). Thus, whereas a larger negativity associated with intensity increments may reflect N1 enhancement, increased negativity following intensity

decrements can only be interpreted as reflecting a genuine MMN response.

Methods

Subjects

Eight subjects slept for a single night in the sleep laboratory. One subject was excluded from the analysis because not enough data were obtained during sleep. The remaining subjects consisted of four males and three females (aged 19-31; mean = 22.0 years). Participants were undergraduate students at the University of Amsterdam. All were experienced sleep laboratory subjects, tested for normal hearing, and who suffered from no medical or psychiatric disorder. Subjects were asked to abstain from caffeine, alcohol, and drug use[5] for twenty-four hours prior to the study. Written, informed consent was obtained prior to the study and an honorarium was offered as compensation.

Procedure

A single auditory stimulus condition was used involving three stimuli differing in intensity: (1) 70 dB SPL "standards", (2) 80 dB SPL increment deviants, and (3) 60 dB SPL decrement deviants. All stimuli were 1000 Hz tones having a total duration of 50 ms and a rise/fall time of 5 ms. The inter-stimulus interval (ISI) was 600 ms. Stimuli were presented randomly in blocks consisting of 1200 trials. The probability was 0.8 for standards and 0.1 for each of the deviants. Deviant stimuli were separated in the train by at least two

[5]The use of "soft drugs" (marijuana, hashish) is not illegal in the Netherlands.

standards.

Stimuli were presented via an earphone inserted in the left ear. Recordings were conducted in a sound-attenuated sleep chamber. Waking ERPs were recorded as subjects read quietly with instructions to ignore the acoustic stimuli. ERPs were also recorded throughout the subsequent sleep period during sleep stages 2 and REM. Sleep stages were identified using the continuous EEG tracings and scored according to the standardized criteria of Rechtschaffen and Kales (1968). A minimum of two to three complete blocks of trials were collected during each sleep stage. The presentation of stimuli was either paused or discontinued when the EEG pattern indicated a sleep stage change, movement or arousal.

Physiological Recording

EEG was recorded using gold electrodes placed at four midline scalp sites: Fz, Cz, Pz, and Oz, and three right hemispheric sites labelled R1, R2, and R3 which were three equidistant points extending in a line from Fz down to and including the right mastoid. The right lateral sites were chosen because the MMN has been shown to be larger over the right hemisphere (Giard et al., 1990; Paavilainen et al., 1991). The EEG electrodes were referenced to an electrode placed on the tip of the nose. In addition, electrodes were placed at the outer canthus of each eye to measure horizontal eye movements and at the supraorbital and infraorbital ridges of the left eye for vertical eye movements. The electrodes were attached collodion-soaked gauze on the scalp and tape on other areas. All impedances were below 5 kOhms. The EEG and EOG were recorded continuously at a sampling rate of 250 Hz and stored on hard disk for later off-line analysis. The time constant was set at 2 s and

the high frequency filter set at 35 Hz. EEG and EOG data were also recorded on a polygraph for the purpose of visual sleep staging.

The off-line sweep time was 500 ms which included a 50 ms pre-stimulus baseline period. During wakefulness, trials in which the EEG or EOG exceeded ± 100 μV were rejected from the average. During sleep the artifact reject was set to $\pm$ 150 μV. Therefore, high amplitude frontal K-Complexes often seen in NREM were rejected. The standard and deviant average waveforms for each condition were digitally filtered using a bandwidth of 3.0 to 20.0 Hz (3 dB roll-off). The choice of such unusually narrow bandwidth was a compromise which served to attenuate the effects of the large slow delta waves occurring in sleep which overlapped the MMN and to "smooth" the waveform by removing superimposed fast activity (see Loewy et al., Appendix A).

Statistical Analysis

"Difference" waves were calculated by subtracting, point by point, the standard from the deviant waveforms at each electrode site in the same condition. The 450 ms post-stimulus sweep period was divided into nine 50 ms intervals beginning immediately after stimulus onset. Within each of these intervals, the average of all data points was computed, yielding an average amplitude measure. This scoring method has been adopted by a number of MMN researchers (see, for example, Alho et al., 1986; Alho et al., 1989). Confidence intervals were computed for each of the nine latency intervals to determine if there was a significant MMN-like negativity present in any of these time points. This procedure determined whether the probability of the mean value of a particular interval fell within an

upper or lower range. If the lower limit was significantly less than 0 μV (i.e., was negative), the interval was considered to contain a MMN. This procedure is equivalent to computing a t-test between the deviant and standard waveforms (Winer, 1971). The literature indicates that the MMN shows a negative polarity at fronto-central sites. A negative directionality was therefore predicted and a one-tailed test of significance ($p < .05$) was applied to the confidence intervals. To restrict the likelihood of chance findings, the latency and scalp distribution of putative MMNs had to conform to that reported in the literature. Accordingly, the frontal or central deflections had to be larger (i.e., more negative) than the parietal site. In addition, the MMN had to occur within a 100-300 ms time window. Finally, the difference wave had to show a polarity inversion at the mastoid location (R3) for the corresponding interval.

Results

Increment Deviance

The grand average waveforms to the standard and deviant stimuli for all subjects in the increment deviance condition are presented in Figure 4.1. During wakefulness, the standard tones elicited a small amplitude N1-P2 complex at about 120 and 170 ms respectively. The deviant increments elicited a broad fronto-central negativity extending from approximately 100 to 400 ms. The difference waves (deviant minus standard) appear at the bottom of the figure. A large amplitude, long-lasting negative difference wave was evident. At the Cz and Fz electrodes, two peaks were observed within this negativity at

approximately 120 and 330 ms. The mean amplitudes of the difference waves for Fz, Cz and R3 electrodes are presented by interval in Table 4.1. The first peak, representing a possible MMN, was associated with a significant ($p < .05$) fronto-central negativity, in the expected latency range at 100-200 ms at and showed polarity inversion at the mastoid location (R3). The second peak was also characterized by a significant ($p < .05$) fronto-central negativity. This wave extended throughout the range of 300 to 450 ms. It showed a delayed polarity inversion at the mastoid during the 400-450 ms interval.

---------- Insert FIGURE 4.1 & TABLE 4.1 About Here ----------

During REM sleep, the grand average waveform showed a small N1-P2 complex for both the standards and the increment deviants. A second, and more prominent negative wave peaked at approximately 300 ms. In the difference wave, a significant ($p < .05$) fronto-central negativity appeared in the 300 to 350 ms interval (see Table 4.1). This was associated with a polarity reversal at the mastoid. The amplitude of this wave was attenuated relative to the late negativity seen in the waking difference wave, but this difference was not significant. A small fronto-central negativity was observed in the 100-200 ms latency range. This negativity did not however attain statistical significance. Moreover, it did not invert in polarity at the mastoid.

During Stage 2 sleep, a large slow *positivity* was evident in the grand averages for deviants and standards throughout the first 300 ms following stimulus onset. The early 100-200 ms negativity following the deviants was not present. A very large and significant

($p < .05$) negative wave extending from 300-400 ms was evident in the difference wave (see Table 4.1). This negativity showed a centro-parietal distribution. It did not however show a polarity inversion at the mastoid site.

Decrement Deviance

The grand average waveforms to the lower intensity-deviant stimuli are presented in Figure 4.2. When subjects were awake, the deviants elicited a broad negativity with the same duration as that seen for the intensity-increments, but with a reduced amplitude. In the difference wave, a dual-peaked fronto-central negativity was again apparent but the amplitude of these peaks was attenuated relative to wakefulness. The mean amplitudes for the intensity decrements are presented by interval in Table 4.2. None of the intervals in the difference wave significantly differed from baseline. Moreover, no polarity inversion at the mastoid was observed for either peak.

---------- Insert FIGURE 4.2 & TABLE 4.2 About Here ----------

The REM sleep grand average waveform for intensity decrements was near baseline for the entire post-stimulus period and, therefore, showed no evidence of any negative-going deflections. No significant negativities were observed in the difference wave (see Table 4.2). The grand average waveform for Stage 2 sleep also showed a large *positivity* during the initial 300 ms following stimulus onset. There was no evidence of either an early 100-200 ms or a later 300-400 ms negativity.

The difference wave for intensity increments and decrements during wakefulness and REM sleep are superimposed in Figure 4.3. For increments, it can be seen that the earlier peak at approximately 150 ms seen in wakefulness is much attenuated in REM. The second peak in wakefulness, at approximately 350 ms, is however only slightly attenuated in REM. For the decrement deviants, two peaks are still evident in wakefulness at the same latencies seen for increments (150 and 350 ms, respectively). These however were non-significant. During REM, the decrement difference wave shows a single peak which was very early and very low amplitude at approximately 80 ms. This wave was also not significant.

---------- Insert FIGURE 4.3 About Here ----------

Discussion

When subjects were awake and reading, a long-lasting negativity was elicited by higher intensity deviant tones. The negative wave showed a maximum amplitude at fronto-central sites and appeared to consist of two separate subcomponents. The first occurred in the expected MMN latency range (between 100 and 200 ms) and was associated with polarity reversal at the mastoid. It represents, therefore, a possible MMN candidate. It is also possible however that this negativity was a result of an enhancement of the N1. A stimulus intensity increases, the amplitude of N1 amplitude also increases and then saturates (Näätänen & Picton, 1987). In the deviant grand average for wakefulness (Fig. 4.1), a seemingly enhanced N1 is visible at approximately 100 ms. It is most prominent at the Fz,

Cz, and Pz electrodes. The polarity inversion at the mastoid (R3), which likely corresponds to the MMN, does not occur until approximately 200 ms. Thus the initial negative subcomponent (at 100-200 ms) of the difference wave for intensity increment deviants probably reflects the temporal and spatial summation of both an enhanced N1 and the MMN.

The second subcomponent peaked in the 350 to 400 ms interval. This late wave also showed a fronto-central distribution and a polarity inversion at the mastoid site, consistent with the MMN. It occurred however much later than the MMNs reported in other studies conducted on awake subjects (see Näätänen, 1992 for a review). Näätänen et al. (1987) recorded a small amplitude MMN to slight intensity increments (84 dB deviant, 80 dB standard). Their MMN appeared as a single peaked negativity at approximately 250-300 ms. The longer peak latency of their MMN is probably attributable to the use of a smaller intensity separation condition than that used here. The sweep time used by Näätänen et al. (1987) was only 300 ms. Thus it cannot be determined whether a later 350-400 ms peak, such as the one seen in the present study, was also elicited.

The later negative component observed in the present study might reflect the N2b process. The N2b is usually seen in "attend" conditions, but may appear to unattended stimuli that are "obtrusive" or difficult to ignore (Näätänen et al., 1982; Loveless, 1986). This may have been true of the stronger intensity increment deviants. The N2b however usually appears much earlier than 350-400 ms. Näätänen et al. (1993) described the appearance of N2b in "attend" conditions to intensity *decrements* as being superimposed on the MMN at approximately 250 ms. This would more closely correspond with the earlier peak in the present waveform. Moreover, N2b does not show polarity inversion at the

mastoid (Sams et al., 1985; Näätänen et al., 1989), whereas the late peak observed here did show such an inversion.

The evoked potential to the deviant increments was also characterized by a sustained negativity which appeared to be superimposed across both negative peaks. A similar type of negativity was also evident in the waveforms presented by Näätänen et al. (1987) for unattended intensity increments. Although the continuation of this negativity could not be observed (due to the short sweep), it is apparent in their Figure 1 that the MMN did not return to baseline at the end of the analysis period.

The lower intensity deviants elicited a negative wave during wakefulness that was morphologically similar to that elicited by the higher intensity deviants. The decrement deviance difference wave was characterized by two peaks occurring in the 150-200 and 350-400 ms latency intervals. These corresponded very closely to the negative peaks seen for increments. The negative deflections for decrements did not however attain statistical significance, and showed only a slight trend toward inversion at the mastoid. As in the case of the increments, the appearance of the second negative peak for intensity decrements is difficult to interpret in light of previous studies (Näätänen et al., 1987; Alho et al., 1989; Näätänen et al., 1989; Winkler et al., 1990; Paavilainen et al., 1991; Näätänen et al., 1993). which have used short sweep times (ranging from 300 to 400 ms). Snyder & Hillyard (1976) recorded evoked potentials to intensity decrements and but used a longer sweep time (600 ms). In their Figure 1, two negativities may be observed at approximately 225 ms and 330 ms in the grand average waveforms for unattended deviants (deviant-standard difference waves were not presented). The authors interpreted the first peak as reflecting a "mismatch

process". The second peak was labelled "N3" but its significance was not discussed. The two negative peaks were separated by a P3a component.

The failure to elicit a MMN, that was significantly larger than baseline levels, to intensity decrements in wakefulness contrasts with previous findings reported in the literature (Näätänen et al., 1987; Näätänen et al., 1989; Paavilainen et al., 1991). In these studies, MMNs to intensity decrements were recorded while subjects were instructed to read a book and ignore the tones. In each case, an 80 dB standard was used and significant MMNs were obtained from the presentation of decrements ranging from 74 to 57 dB. In the present study, 70 dB standards and softer 60 dB deviants were used. Because the decibel scale is logarithmic, the acoustic energy loss in a decrement from 70 to 60 dB is less than from 80 to 70 dB, and much less than 80 to 57 dB. The smaller MMN observed in the present study to the 10 dB decrement may thus be reflective of a reduced standard-deviant energy difference.

Only a small, attenuated and non-significant early (100-200 ms) negativity was observed in REM sleep. This is in contrast to findings concerning frequency deviants. Loewy et al. (in press) reported an attenuated but significant MMN to frequency deviants during REM sleep. These differences between frequency and intensity MMNs are however consistent with the attentional literature. The frequency MMN is much less affected by the direction of attention than the intensity MMN (Näätänen, 1991; Woldorff et al., 1991; Näätänen et al., 1993). During Stage 2 sleep, there was no evidence of the early negativity for increment deviants. This is consistent with the majority of previous studies which reported that the MMN to frequency deviant stimuli is not present in Stage 2 sleep (Paavilainen et al., 1987; Nielsen-Bohlman et al., 1991; Loewy et al., in press). An

exception is the study by Campbell et al. (1992) who observed a greatly attenuated, but non-significant, MMN to frequency deviants in Stage 2 sleep. The inability, in many instances, to elicit an intensity MMN during Stage 2 may be explained by the greater sensitivity of the MMN to intensity changes relative to that for frequency changes.

Näätänen and colleagues (Näätänen et al., 1991; Näätänen et al., 1993) have proposed that the MMN is generated by two populations of neurons in the supratemporal plane of the auditory cortex. The first, referred to as *computational* neurons, automatically elicit the MMN when a mismatch is detected. The second type, referred to as *amplifying* neurons determine the magnitude of the response. This in turn may trigger the activation of frontal mechanisms leading to the *perception* of stimulus change. Näätänen et al. (1991) suggested that the attenuation of the MMN amplitude for intensity in waking selective-attention conditions may be attributed to a suppression of the MMN-generating process, rather than the antecedent sensory or storing functions. That is, the threshold for the elicitation of the intensity-MMN, like the frequency MMN, is not affected by attention. Rather, the activity of the amplifying system is affected. During Stage 2 and REM sleep, it would however appear that even the computational system for the intensity MMN is suppressed. It is, of course, possible that the computational system remains functional during sleep but that the amplifying system is so affected that the MMN does not exceed background noise levels.

A late negativity, similar to that seen in wakefulness, was observed for increments in REM sleep appearing in the 300 to 400 ms window. This negativity was largest at frontal and central locations and showed polarity inversion at the mastoid site in these intervals. It thus met the topographical criteria for the MMN. It occurred however much later than the

MMNs reported in the literature. Because the MMN reflects a sensory memory comparison between the deviant stimulus and the preceding standard, the peak latency of the MMN becomes longer as the inter-stimulus interval (ISI) is increased. Eventually, the response decays entirely. The longest ISI reported thus far to elicit the MMN is 10 s (Böttcher-Gandor & Ullsperger, 1992). Even when this long interval was used, the peak latency of the MMN did not exceed 300 ms. In the present study, stimuli were presented at a considerably faster rate (600 ms). It would therefore be very difficult to interpret the late negativity recorded for the intensity increments as a genuine MMN response.

The lower intensity deviants did not elicit any significant negativities in REM sleep. This is consistent with the waking data in which no significant MMN was obtained for the decrement deviants. In addition, the absence of a late negativity for decrements argues against the interpretation of the late peak for increments representing a true mismatch process. If the negativity was attributable to the occurrence of a mismatch between the deviant and the standard, a peak should have also been evident in the decrement waveform. An explanation for this late negativity is that it is due to the N350 process. The N350 is typically seen in NREM sleep and may precede the evoked K-Complex. The K-Complex may be elicited by loud abrupt auditory stimuli (Campbell & Bastien, 1994). Campbell et al. (1992) have reported data suggesting that a small amplitude N350 may appear in REM sleep. Small amplitude N350s may have been elicited by the loud deviants and included in the average for REM sleep.

A large amplitude negative deflection was also elicited by the increment deviants in the 300 to 400 ms intervals in Stage 2 sleep. Other authors have also reported negativities

occurring in the 300 to 350 ms latency range to deviant auditory stimuli presented in NREM sleep (Harsh et al., 1994; Nielsen-Bohlman et al., 1991; Salisbury & Squires, 1992; Winter et al., 1995). Unlike the negativity observed in REM, the late negative wave in Stage 2 was largest at the central and parietal electrodes and did not show polarity reversal at the mastoid. It probably does not therefore represent a MMN. It may reflect an early component of the evoked K-Complex. The K-Complex consists, in part, of two negative peaks occurring at approximately 350 and 550 ms (Bastien & Campbell, 1994; Halász et al., 1985). The large amplitude N550 is easily detected in single trials. A visual inspection of the continuous EEG indicated that the K-Complex (in this case the N550 component) was not often elicited by the deviant stimulus. Nevertheless, the N350 wave occurs whether the N550 is elicited or not (Campbell & Bastien, 1994).

		1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
AWAKE	**Fz**	0.28 (0.66)	-0.10 (0.53)	-1.51* (0.70)	-2.17* (1.33)	-2.13* (1.55)	-2.17* (2.24)	-2.51* (2.26)	-2.15* (2.09)	-0.78* (0.55)
	Cz	0.37 (0.64)	-0.19 (0.51)	-1.68* (0.80)	-2.05* (1.17)	-1.73* (1.79)	-1.83 (2.32)	-2.28* (1.98)	-1.58* (1.19)	-0.58* (0.50)
	R3	-0.10 (0.53)	-0.14 (0.64)	0.13 (0.63)	0.34 (1.16)	-0.09 (1.45)	-0.05 (1.57)	-0.05 (1.60)	0.48 (1.22)	0.00 (0.55)
REM	**Fz**	0.03 (0.45)	-0.24 (0.75)	-0.33 (0.99)	0.06 (2.09)	-0.12 (2.11)	-1.11 (1.74)	-1.57* (0.93)	-0.75* (0.68)	-0.30 (0.39)
	Cz	-0.15 (0.62)	-0.35 (0.99)	-0.43 (1.33)	-0.19 (2.56)	-0.49 (2.34)	-1.41 (1.92)	-1.80* (0.99)	-0.86* (0.75)	-0.31 (0.54)
	R3	-0.11 (0.29)	-0.25 (0.28)	-0.24 (0.43)	-0.07 (0.57)	-0.09 (0.85)	-0.22 (0.80)	0.06 (0.89)	0.22 (0.71)	0.08 (0.38)
STAGE 2	**Fz**	0.64 (0.67)	1.04 (0.78)	1.10 (1.01)	1.63 (1.47)	1.21 (1.81)	0.26 (1.59)	-1.57 (1.76)	-2.07* (2.17)	-0.95 (1.40)
	Cz	0.74 (0.49)	1.37 (0.98)	1.26 (1.41)	2.13 (1.55)	1.73 (2.06)	-0.62 (1.39)	-3.96* (2.79)	-4.27* (3.76)	-1.62 (1.78)
	R3	0.12 (0.14)	0.04 (0.47)	-0.06 (0.14)	0.01 (0.67)	-0.07 (0.92)	-0.51 (1.07)	-0.80 (1.09)	-0.59 (0.99)	-0.17 (0.42)

Table 4.1

Increment deviance: Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 450 ms sweep (n=7). * denotes negative amplitude values significantly different from baseline ($p < .05$).

		1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
AWAKE	**Fz**	-0.15 (0.68)	-0.06 (0.99)	-0.41 (1.61)	-1.10 (1.86)	-0.64 (1.87)	-0.16 (1.06)	-0.80 (1.32)	-1.00 (1.81)	-0.47 (0.71)
	Cz	-0.22 (0.56)	0.14 (1.00)	-0.08 (1.06)	-1.11 (1.63)	-0.34 (1.37)	0.17 (0.95)	-0.44 (1.07)	-0.56 (1.46)	-0.33 (0.64)
	R3	0.11 (0.44)	0.00 (1.26)	-0.23 (1.43)	-0.31 (2.00)	-0.28 (1.60)	-0.39 (1.30)	-0.17 (1.54)	-0.21 (1.56)	-0.16 (0.87)
REM	**Fz**	-0.31 (0.65)	-0.76 (0.99)	-0.54 (1.03)	-0.53 (1.12)	-0.38 (0.78)	0.47 (1.62)	0.64 (2.46)	0.31 (2.34)	0.07 (1.20)
	Cz	-0.39 (0.36)	-0.73 (1.02)	-0.54 (1.17)	-0.53 (1.37)	-0.20 (1.62)	0.42 (2.16)	0.50 (2.40)	0.01 (2.27)	-0.02 (1.18)
	R3	-0.06 (0.26)	0.19 (0.48)	0.08 (0.59)	0.02 (0.68)	0.09 (1.07)	-0.05 (0.84)	-0.16 (0.69)	-0.04 (0.85)	-0.04 (0.46)
STAGE 2	**Fz**	0.26 (0.75)	0.08 (0.72)	0.47 (0.87)	1.13 (1.40)	1.21 (1.60)	1.39 (1.62)	1.37 (1.15)	1.10 (1.49)	0.54 (1.12)
	Cz	0.50 (1.19)	0.34 (1.49)	0.52 (1.62)	0.78 (1.55)	0.79 (1.83)	0.84 (2.24)	0.63 (1.73)	0.39 (1.84)	0.03 (1.23)
	R3	-0.07 (0.36)	0.17 (0.38)	0.23 (0.73)	-0.23 (0.77)	-0.44 (1.00)	-0.48 (1.09)	-0.57 (0.88)	-0.65 (0.91)	-0.33 (0.53)

Table 4.2

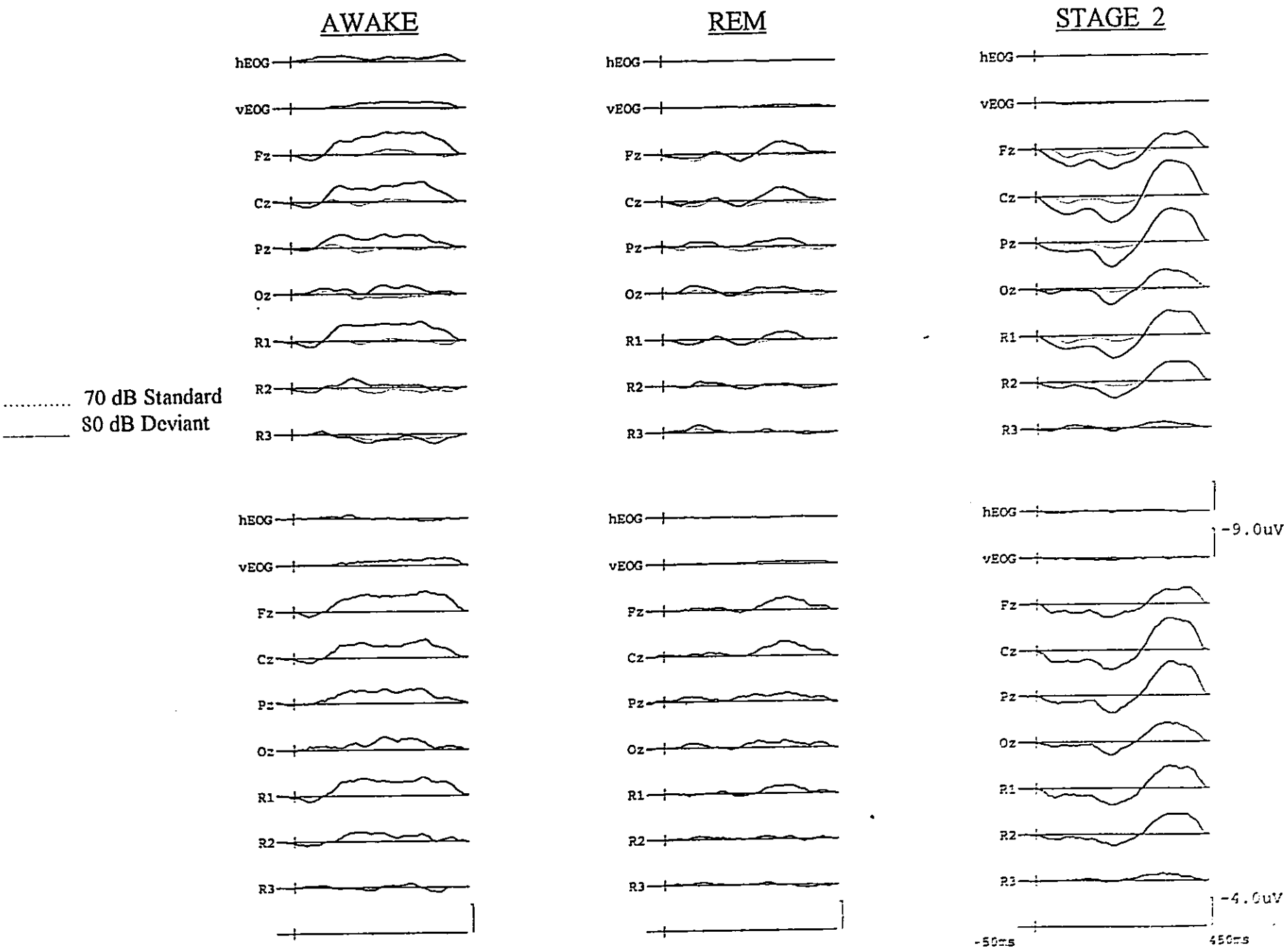
Decrement deviance: Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms for each 50 ms interval of the total 450 ms sweep (n=7). * denotes negative amplitude values significantly different from baseline ($p < .05$).

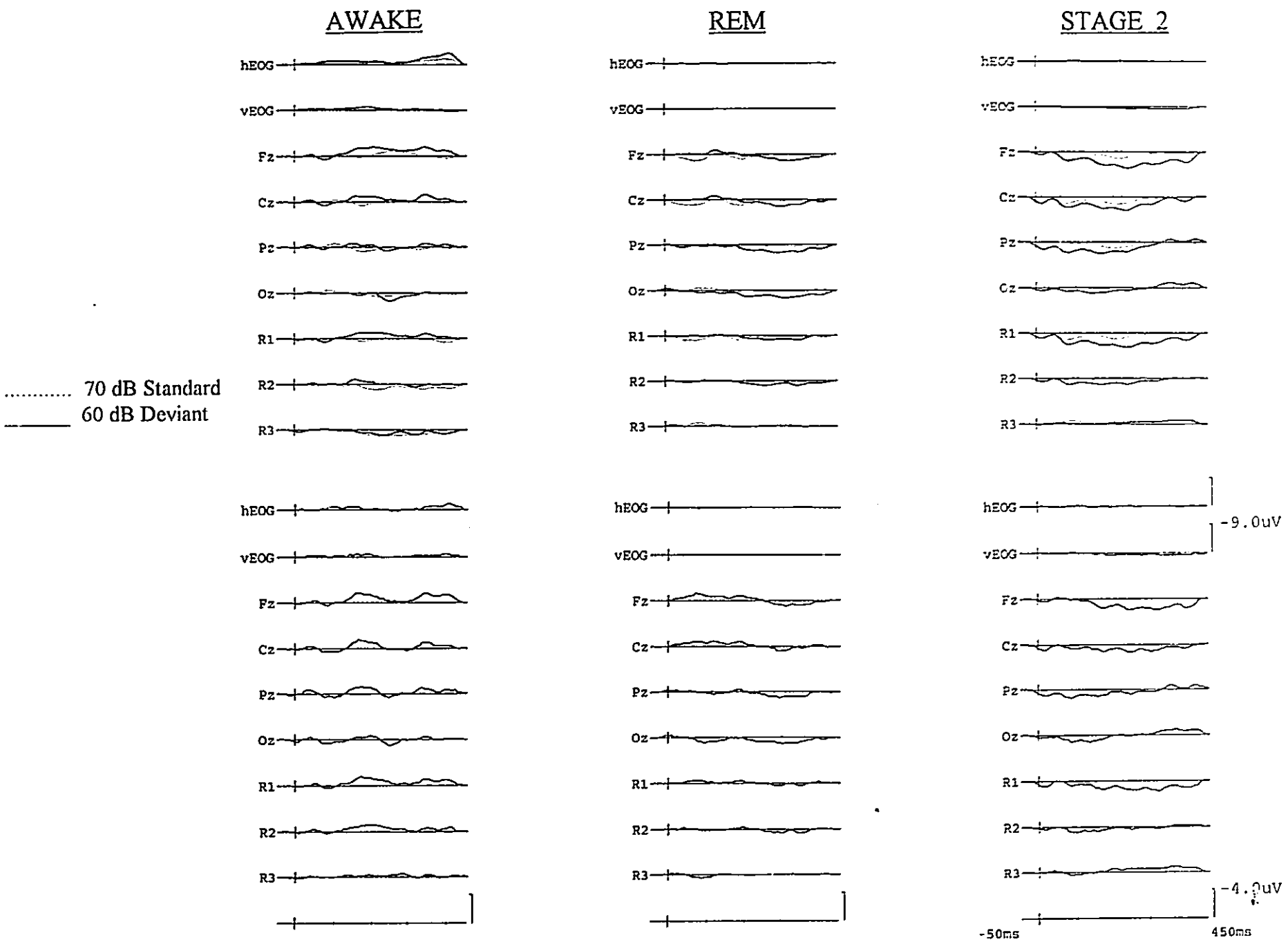
Figure Legend

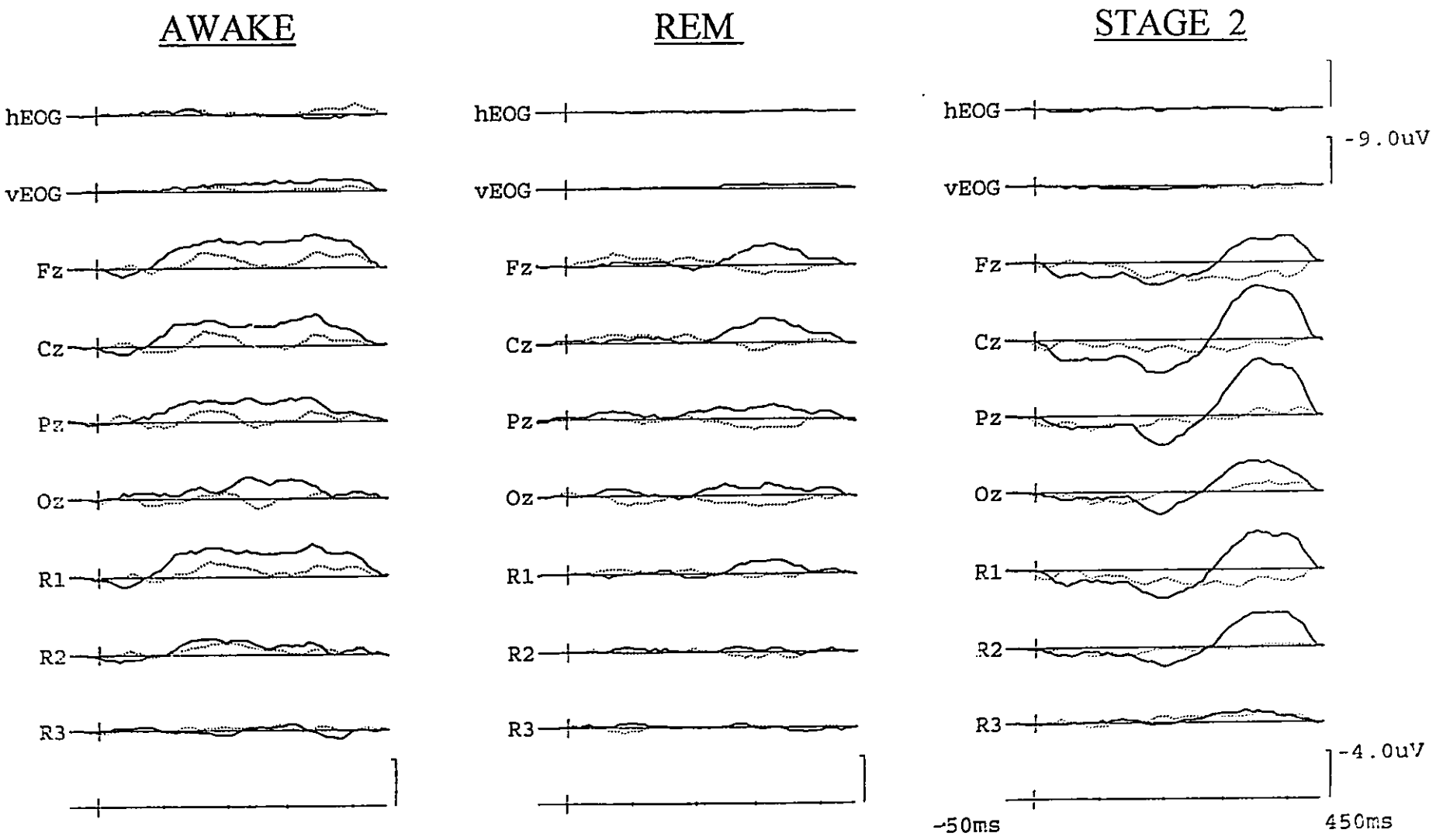
Figure 4.1. Increment deviant (80 dB) and standard (70 dB) grand average waveforms for Awake, REM, and Stage 2. Deviant-standard difference waveforms appear in the lower portion.

Figure 4.2. Decrement deviant (60 dB) and standard (70 dB) grand average waveforms for Awake, REM, and Stage 2. Deviant-standard difference waveforms appear in the lower portion.

Figure 4.3. Difference waves (deviant - standard) for Awake, REM, and Stage 2 for increment (70 dB) and decrement (60 dB) deviant conditions.


AWAKE
REM
STAGE 2
70 dB Standard
80 dB Deviant
hEOG
vEOG
Fz
Cz
Pz
Oz
R1
R2
R3
-9.0uV
-4.0uV
-50ms
450ms


AWAKE
REM
STAGE 2
hEOG
vEOG
Fz
Cz
Pz
Oz
R1
R2
R3
..... 70 dB Standard
_____ 60 dB Deviant
-9.0uV
-4.0uV
-50ms
450ms


AWAKE
REM
STAGE 2
hEOG
vEOG
Fz
Cz
Pz
Oz
R1
R2
R3
-9.0uV
-4.0uV
-50ms
450ms
..... 60 dB Deviant
_____ 80 dB Deviant

Chapter 5

General Discussion and Conclusions

The present thesis investigated the presence of the mismatch negativity (MMN) in sleep. The MMN is a negative component of the human auditory evoked potential (AEP) that is elicited by the presentation of an infrequent, physically deviant stimulus occurring in a series of frequent homogeneous stimuli. The majority of previous studies conducted on awake subjects indicate that the MMN is highly resilient to the effects of attention. One means of assessing the attentional independence of the MMN is to record it during sleep, a state where subjects may be least conscious of their external environment. Three experiments were conducted in which the auditory stimulus parameters of frequency, duration, and intensity were manipulated.

Summary of Findings

In experiment 1, auditory stimuli deviating in frequency elicited a distinct MMN during wakefulness, as subjects read quietly with instructions to ignore the tone presentations. In the large frequency deviant condition, 2000 Hz deviant tones presented infrequently in a train of 1000 Hz standards, elicited a MMN occurring in the 100-200 ms intervals following stimulus onset. In the small frequency deviant condition, 1050 Hz deviant tones elicited a MMN in the 100-200 ms intervals. The MMN elicited by the small deviants was reduced in amplitude relative to the MMN for large deviants. These findings are consistent with previous studies which have shown the MMN to be larger in amplitude

and have a shorter latency for larger magnitudes of stimulus deviance (Sams, Paavilainen et al., 1985; Novak et al., 1990). The observed negativities were judged to be genuine mismatch responses because they conformed to the criteria for the MMN specified in the literature such that they: (a) occurred in the expected latency range of 100-300 ms, (b) showed a fronto-central maximum amplitude, and (c) showed a posterio-temporal decline in amplitude and ultimately reversed polarity (i.e., showed a positive-going deflection) at the mastoid when a reference at the nose was employed.

During REM sleep, significant negativities were observed in the expected MMN latency range for both large and small frequency deviants in the 100-150 ms intervals. The MMN amplitude for large deviants was attenuated relative to that seen in wakefulness, whereas the MMN amplitude for the small deviants was not reduced. The only observed latency difference occurred for the small deviant MMN which peaked approximately 50 ms earlier than in waking. The finding of a MMN in REM to stimuli deviating in pitch replicates the earlier finding of Campbell et al. (1992) who also found a small amplitude MMN in REM for 2000 Hz deviants, presented with 1000 Hz standards. In the present study, very slight deviations in pitch (1050 vs. 1000 Hz) also elicited the MMN in REM. During both the early and late phases of Stage 2 sleep, small amplitude negativities were observed for both types of deviants occurring between 50-150 ms. None of these were however significantly above baseline. The negativity for the large deviants did show a scalp representation consistent with the MMN. It was largest at frontal and central electrodes an inverted at the mastoid. No MMN-like waves were observed in Stage 4 sleep for either large or small frequency deviants. The failure to record an MMN in NREM sleep is

consistent with the majority of other studies which have examined auditory stimulus deviance in sleep (Paavilainen et al., 1987; Nielsen-Bohlman et al., 1991; Winter et al., 1995). Sallinen et al. (1994) reported a MMN in Stage 2 on trials in which a K-Complex was elicited by the deviant stimulus. In the present study however, an insufficient number of K-Complexes were elicited by the deviant to permit a comparison of K-Complex and non-K-Complex trials.

In experiment 2, tones deviating in duration also elicited a MMN in a waking reading condition. In the increment deviant condition, 150 ms deviant tones, when presented with 100 ms standards, elicited a significant fronto-central negativity lasting throughout the 150-300 ms interval range. The MMN, peaking in the 200-250 ms interval, comprised a portion of this wave. A later negative component overlapped the MMN but did invert at the mastoid. It may represent the frontal component of the MMN, revealed by Giard et al. (1990), which does not invert at the mastoid. Another possibility is that it represents the superimposition of N2b which also does not show such inversion. The latter possibility is more likely because of the presence of an associated P3a. Thus these deviants may have been difficult for the subjects to completely ignore. In the decrement deviant condition, short 50 ms deviants also elicited a fronto-central MMN in the 150-200 ms interval. This wave was also associated with a sequential but overlapping negative component, possible reflecting an N2b. It was evident in the difference waves (see Fig. 3.3), that the peak of the MMN to the decrement deviants occurred approximately 30 ms earlier than the MMN for the increments. This shift in latency is consistent with previous reports that short duration deviants will elicit an earlier MMN than long duration deviants, when presented in conjunction with a standard

stimulus of constant duration (Näätänen et al., 1989). In the present study, the detection of the 150 ms deviant could not begin until the offset of the 100 ms standard, whereas detection of the 50 ms deviant could begin at its offset. N1 amplitude did not differ between the two types of deviants. The increased negativity for deviant stimuli was not due to an enhancement of N1 because the latency of N1 was the same both increments and decrements, whereas the latency of the MMN varied between conditions. This effect also showed that the increased negativity for deviants was not due to the sustained negativity elicited by longer duration tones. This is because the negativity was greater for the 50 ms deviants than for the longer 100 ms standards.

During REM sleep, no statistically significant negativities were observed in the difference waves for either increment or decrement deviants. However, a small negative wave was observable for increments at 250-300 ms and for decrements at 150-200 ms. These latencies are consistent with the "temporal shift" shown previously (Näätänen et al., 1989) to characterizes the MMN in wakefulness for long and short duration deviant tones. The latencies of these negativities also showed a strong temporal correspondence to the MMNs recorded in the present waking conditions (150-300 ms for increments and 150-250 ms for decrements). Moreover, both negativities were largest over fronto-central regions and inverted at the mastoid. There were no potential MMNs evident in any of the NREM sleep stages. These findings are unique because no laboratories had previously examined ERPs to duration deviant tones in sleep. The negativities observed in REM exhibited latency and topographical characteristics, consistent with the MMN. It is possible that the MMN to duration changes persists in REM sleep but is much attenuated. The duration MMN may

therefore be more susceptible to attentional effects than MMN for frequency deviance.

In experiment 3, 80 dB intensity increments elicited a long-lasting fronto-central negativity during wakefulness which lasted throughout the 100-450 ms intervals. This negativity was comprised of an early negative component at 100-250 ms and a later negative component at 300-400 ms. There was an associated polarity inversion at the mastoid site for both of these components. For the 60 dB intensity decrements, two fronto-central negative components were still evident at 150-200 and 300-400 ms. These however were not significantly above baseline and showed no polarity inversion at the mastoid. This finding contrasts with those of previous studies in which the MMN to intensity decrements was recorded during waking, reading conditions (Näätänen et al., 1993; Näätänen, Paavilainen, Alho et al., 1989). The use of relatively lower intensity stimuli in the present study (compared to those used by Näätänen's group) might account for these differences.

During REM sleep, the increment deviants elicited a very small and non-significant negativity in the 100-200 ms intervals. A significant fronto-central negative wave at 300-350 ms was also observed. This later negative wave inverted at the mastoid. It may correspond to the negativity observed in wakefulness at 300-400 ms or it may reflect a sleep-specific process. For the decrement deviants, no significant negativities appeared in the difference wave. Only a very attenuated early peak appeared at 50-100 ms. This wave did however show polarity inversion at the mastoid. During Stage 2 sleep, increment deviants elicited a large late negative peak at 300-400 ms. This wave showed a more posterior scalp distribution than that expected for the MMN and did not invert at the mastoid. Similarly, its representation on the scalp is not consistent with the late negativity seen in REM, and

therefore these two negative waves probably represent separate processes. The Stage 2 negativity may represent the N350 component of the evoked K-Complex (Bastien & Campbell, 1992).

Discussion

The findings obtained from the three studies suggest that the MMN *is* influenced by the subject's conscious state. Of the stimulus parameters examined, the frequency MMN appeared to be the most resilient to the effects of sleep, in that it persisted in REM sleep, whereas the duration and intensity MMNs were not evident in this stage. The MMN to all three types of stimulus change appeared to be absent in NREM sleep. Thus, NREM sleep appears to be associated with a strong attenuation of the MMN. This conclusion appears to conflict with the view of Näätänen and colleagues that the MMN is an *automatic* sensory memory comparison process. The view of the MMN as an obligatory sensory component is based on the findings of early studies using alert and awake subjects indicating that the MMN was elicited regardless of attentional state or task demands. These studies showed that deviants presented to "to-be-attended" and "to-be-ignored" channels elicited MMNs of equal magnitude (see review by Näätänen, 1992). Subsequent studies however (Alho et al., 1992; Woods et al., 1992) have reported evidence of an attenuation of the frequency MMN under conditions involving attentional withdrawal. In addition, the previous finding of an attenuated intensity MMN in wakefulness, when attention is strongly re-directed to another channel, (Woldorff et al., 1991; Näätänen et al., 1993) also indicates a possible attentional affect on the MMN.

A model of MMN generation has been proposed by Näätänen (1993) which may account for these findings of attentional modulation of the MMN. He postulated the existence of two types of functionally distinct neuronal populations, located in primary auditory cortex, responsible for the elicitation of the early supratemporal component of the MMN. The first are *computational* neurons which generate the initial mismatch signal by responding to even the slightest stimulus changes. The second are *amplifying* neurons which receive the signal from the computational neurons and amplify it. The degree to which the signal is amplified depends upon the level of arousal in the cortex. (i.e., decreased arousal is associated with decreased MMN amplitude). Thus the amplifying neurons account for variations in MMN amplitude due to vigilance states or drug effects. It has been shown, for example, that drugs exerting an excitatory influence on the cortex enhance the MMN (Born et al., 1986; Born, Bother et al., 1987), whereas drugs which have an inhibitory influence attenuate the MMN (Born, Kern et al., 1987). Näätänen contends that the supratemporal component of the MMN is sensory-specific and that it is automatically elicited by computational mechanisms. The amplitude of the supratemporal component may vary however, due to differential excitability of the amplifying system. The presence of two subcomponents for the supratemporal MMN is supported by the dipole source analysis of Scherg et al. (1989) and current source density analysis of Giard et al. (1990). Both studies reported the presence of two generator sources for the supratemporal MMN. An additional element of Näätänen's model concerns the late frontal component of the MMN revealed by Giard et al. (1990). He proposed that when the amplification of the supratemporal MMN reaches a certain "threshold" level, the late frontal component may be activated. The

activation of the frontal component may signify a "switching of attention" toward the deviant stimulus leading to the conscious detection of it. This mechanism may also be closely related to the Orienting Response (Sokolov, 1975).

The results of the present studies concerning the effects of sleep on the elicitation of the MMN might be explainable in terms of this model. It may be useful to first consider the variations in cortical arousal, subjective experience and responsivity to external stimulation that are associated with the different wake/sleep states. The wake-sleep transition is characterized by marked EEG, subjective, and behavioural changes. The waking EEG (with eyes closed) is characterized by rhythmic alpha frequency activity. Subjects report feelings of relaxation and remain highly responsive to external stimulation. Drowsiness or Stage 1 sleep is indicated by an attenuation of alpha and the emergence of slower theta frequency activity. When queried, subjects will report being "awake" more often than "asleep" in Stage 1 and still remain responsive to external stimulation (Kamiya , 1961), although reaction times may increase (Ogilvie et al., 1992). Stage 2 sleep is characterized by the appearance of phasic EEG events such as spindles and K-Complexes. As elapsed time in Stage 2 increases, the probability that subjects will describe their experience as "sleep" also increases (Kamiya , 1961). Behavioural responding to external stimuli ceases in Stage 2 (Ogilvie et al., 1992; Harsh et al., 1994). In SWS (Stages 3 & 4), the EEG is comprised of highly synchronous, large amplitude delta frequency activity. Subjects almost always report being asleep and behavioural responsivity to external stimuli is absent. Bonnet, Johnson, and Webb (1978) reported that , with increasing sleep depth, larger magnitudes of auditory stimulus intensity were required to awaken subjects. The average arousal threshold values

were 70 dB for Stage 2 and 92 dB for Stage 4. Based on arousal threshold measures, Stage 4 was described as the "deepest" stage of sleep.,

REM sleep represents a physiologically and functionally distinct brain state. The tonic EEG in REM resembles that recorded during Stage 1 sleep. REM sleep may thus be considered as an intermediary state on the continuum of arousal between wakefulness and Stage 2 sleep. The phenomenology of REM sleep involves the frequent recall of dreams. Despite the relatively high level of cortical arousal present during REM, subjects exhibit low responsiveness to external stimulation during this state. Williams et al. (1964) found awakening thresholds to auditory stimuli to be highest in REM sleep followed by SWS. Psychologically "relevant" auditory stimuli may however have differential effects. In his review, Broughton (1982) presented evidence that psychologically "meaningful" auditory stimuli (such as the sound of a crying baby) are however more likely than meaningless stimuli to cause awakenings from REM sleep. In NREM sleep, relevant (names) stimuli more frequently elicit K-Complexes than irrelevant (tones) stimuli (Oswald, Taylor, & Treisman, 1960).

The effects of sleep on the MMN seem to parallel the descent down the arousal continuum from wakefulness, through Stage 2 to SWS. In wakefulness, the MMN was elicited by frequency, duration, and intensity changes. Although no significant MMN-like negativity was observed in Stage 2 sleep for any stimulus condition, a non-significant negativity was observed in early Stage 2 for frequency changes that showed the latency and scalp distribution of the MMN. No MMN-like negativity was observed in SWS for any type of stimulus change. In REM sleep, a MMN was elicited by frequency deviants. Duration

deviants elicited a "trend" toward a mismatch response. These effects may again be explained in terms of Näätänen's model. In particular, the locus of effect for the attenuation of the MMN in sleep may be the amplifying system of the supratemporal component. Sleep may be associated with a decreased excitability or perhaps inhibition of the amplifying component of the MMN. This effect may occur in REM sleep, resulting in the appearance of a smaller amplitude MMN to that seen in wakefulness. It may however occur to an even greater extent in NREM sleep. This interpretation implies that the sensory-specific computational system of the MMN may remain intact, at least in REM sleep. There is little evidence that sensory memory, as reflected by the MMN, remains functional in NREM sleep. Furthermore, due to the suppression of the amplifying system, the threshold for activation of frontal cortical mechanisms is not attained. Consequently, there is no conscious detection of the stimulus. An exception may be the occurrence of a very intrusive (i.e., large intensity) deviant stimulus which may cause the subject to awaken.

An additional interacting variable in this conception appears to be the type of stimulus change. Paavilainen et al. (1991) recorded the MMN during a waking reading condition to each of these types of stimulus deviance: frequency (650 Hz deviant, 600 Hz standard), duration (20 ms deviant, 50 ms standard), and intensity (70 dB deviant, 80 dB standard). They found that a MMN was elicited by all conditions and that it had a right frontal predominance. The MMN appeared to be comprised of two sequential overlapping components: (a) an early component that reversed polarity at the mastoid and (b) a later component that did not reverse polarity at the mastoid. The earlier negativity was interpreted as reflecting the supratemporal MMN component. The later wave may have represented the

summating influences of two different sources. It could have been comprised of the frontal component of the MMN, shown by Giard et al. (1990) not to invert at the mastoid. Or it could have reflected an N2b component. N2b is typically seen when stimuli are attended, but may be seen in "ignore" conditions when deviant stimuli are particularly obtrusive (Näätänen et al., 1982). The authors also reported a notable difference between the three types of MMNs. The difference wave of the frequency deviant showed a larger P3a component than those for either duration or intensity. This constitutes further evidence in support of the presence of N2b negativity, indicating that subjects may have inadvertently attended the stimulus presentations. The presence of P3a further suggests that frequency change is more likely to intrude into conscious awareness than some other forms of stimulus deviance. The reason for this is unclear. There may be a strong "biological relevance" for pitch discrimination in humans, and therefore there is greater sensitivity of auditory sensory receptors for frequency change.

In the present studies, a scalp representation similar to that observed by Paavilainen et al. (1991), was found in the difference waves for the waking MMNs in the frequency and duration deviant conditions. The earlier portion of the MMN showed inversion at the mastoid while the descending aspect of the negativity did not. It was however difficult to distinguish this pattern in the difference wave of the intensity increments because of the superimposition of a sustained negative wave across the sweep. P3a was evident in the waking difference waves in all of the frequency and duration oddball conditions. The MMN may therefore have been involved in the partial activation of frontal generator mechanisms associated with conscious awareness of the deviants. There was no trend toward P3a

elicitation in the intensity difference wave, therefore intensity deviants may have been easier for subjects to ignore. It is possible however that P3a may have been masked by the sustained negativity.

The MMN to frequency changes was evident in REM. A "trend" toward the presence of a duration MMN occurred in REM, but there was no evidence of an intensity MMN in REM. Thus the attenuation of the amplifying system may be greater for duration and intensity than for frequency change. The findings concerning intensity are concordant with studies of awake subjects showing the MMN to intensity change to be the most vulnerable to attentional influence (Woldorff et al., 1991; Näätänen, 1993). The MMN elicited in REM sleep by frequency changes did not show the later negative contribution seen in waking nor P3a. It is possible therefore that only the earlier supratemporal component was generated. Thus, frontal centres, leading to conscious perception of frequency change, may not have been active in REM sleep. The sleep-related attenuation of the amplifying component of the MMN may have been even greater for duration and intensity change during REM. In NREM sleep, the MMN for all three types of stimulus deviance was greatly attenuated. The locus of effect on the MMN of NREM sleep may be either the computational or the amplifying system.

This relationship between the elicitation of the MMN and stage of sleep may be explained in different ways. It is possible that the inability to observe the MMN during NREM sleep may be a confound of the large amplitude background EEG. The amplitude of the EEG increases during the descent from Stage 1 to Stage 4 sleep. As a result, it may be increasingly difficult to extract the very small amplitude MMN through the averaging

process. Optimal filtering settings were employed in an attempt to attenuate the high amplitude delta waves. In these and previous studies, many deviant trials have been presented in an effort to enhance the signal-to-noise ratio and still no MMN was observed in SWS. The apparent absence of the MMN is SWS could still be attributable to a dampening of the amplifying system of the MMN. It is the presence of the small amplitude sensory-specific component that may have been masked by the large amplitude, slow EEG.

An alternative explanation concerns the functional state of the brain. In the present series of studies, the MMN was most likely to be elicited during the REM stage of sleep. A functional similarity may therefore exist between the REM state and wakefulness concerning how deviant auditory stimuli are processed. Some functional links between REM sleep and the waking state have been previously demonstrated. Horne (1988) noted that hippocampal theta activity is present during waking and REM sleep and appears to be related to the directing of "attention" toward novel stimuli. This hippocampal theta rhythm is not evident in NREM sleep. A number of authors have reported a relationship between REM sleep and processes associated with learning and memory consolidation (Crick & Mitcheson, 1983; Horne & McGrath, 1984, Smith & Lapp, 1991). As mentioned, Broughton (1982) reported that subjects may be able to detect salient, relevant events during REM.

Another functional similarity between REM sleep and waking concerns the "40-Hz rhythm" or " 40-Hz response". The 40-Hz rhythm is an EEG frequency (the 'gamma-band') believed to reflect the oscillatory activity of thalamo-cortical neurons. It is comprised, in part, of components of the middle latency responses (10-50 ms) of the auditory evoked potential (Galambos, Makeig, & Talmachoff, 1981). It has been recorded from single cells

as well as in multi-cellular and extra-cellular field potentials (see Llinás and Ribary, 1993). The 40-Hz rhythm is a transient, spontaneous oscillation that is observed predominantly during alert wakefulness. Llinás and Ribary (1993) found that 40-Hz activity, similar to that seen in waking, was also present during REM sleep. This rhythm was however markedly reduced in delta sleep (or SWS). The authors postulated that the spontaneous 40-Hz rhythm may be related to attentiveness/alertness, implying that "consciousness" was present in waking and REM, but not SWS. In addition, they examined the effects of auditory stimulation on the 40-Hz rhythm during these states. Very brief tones, presented in 500 ms blocks and varying in frequency between 150 and 650 Hz, were used. During wakefulness, the tones had the effect of evoking the "40-Hz response" which they described as a "re-setting" of the spontaneous 40-Hz oscillation. The evoked 40-Hz response could not be elicited in either REM or delta sleep. Therefore, during wakefulness, external stimuli can elicit the 40-Hz response which may subserve conscious perception of the stimulus. During the REM state however, subjects may be "attentive" (as indicated by the presence of spontaneous 40-Hz activity) but this attentiveness is directed toward "internal events". Such internal events may be related to dreams which are frequently reported upon awakening from REM sleep. Dreams may also be recalled upon awakening for NREM sleep, however the recall rate is lower and there are distinct qualitative differences, with REM dreams being more visual and vivid (see Koulack, 1991). Due to the subject's attentional involvement in the dream, external (but "irrelevant" in the case of Llinás and Ribary) stimuli may not intrude into this "conscious" experience in such a way that attention is re-directed toward the external event. There is evidence that external events are often incorporated into the content

of the ongoing dream (see review by Broughton, 1982). That a "reflective" form of consciousness may also be present during the REM state is supported by the phenomenon of lucid dreaming (Laberge, 1992). During lucid dreams, subjects purportedly become aware they are dreaming while the dream is happening. Experienced lucid dreamers demonstrate an ability to willfully control the content of the dream. Moreover, these individuals can "signal" this awareness to the experimenter, without any indication of polygraphic awakening. The lucid dreamer is thus quite conscious of the fact they are dreaming. The mentation which accompanies REM sleep, in the form of dreaming, may be related to the presence of the spontaneous 40-Hz rhythm.

Additional evidence that the 40-Hz rhythm is related to attentional processes is derived from ERP studies conducted on awake human subjects. Tiitinen, Sinkkonen, Reinikainen, Alho, Lavikainen, and Näätänen (1993) found that the 40-Hz response elicited by attended tones was greater than that for unattended tones. May, Tiitinen, Sinkkonen, and Näätänen (1994) and Tiitinen, Sinkkonen, May, and Näätänen (1994) examined the relationship between the 40-Hz response and the N1 and MMN components of the AEP. During a long five hour recording session, subjects were presented with a frequency deviant oddball stimulus condition. The authors reported that, over time, the evoked 40-Hz response and the N1 attenuated. They thus postulated that the 40-Hz response, like N1, was a indicator of vigilance state, which declined across the long recording session. Unlike N1 and the 40-Hz response, the amplitude of the MMN did not attenuate across the session. The authors interpreted this finding as a dissociation of MMN from these other processes concerning vigilance states. It may be however that the MMN may is insensitive to

decreases in vigilance within the waking state.

The spontaneous 40-Hz rhythm may represent an electrophysiological indicator of attention. The re-setting of the 40-Hz rhythm, in the form of the "evoked" 40-Hz response, upon external stimulation may reflect a switching of attention toward the eliciting stimulus. This attention switch may involve the activation of frontal cortical mechanisms associated with conscious perception of the stimulus. Näätänen (1992) postulated that the triggering of frontal attentional mechanisms may be subserved by the N1 response, particulary the frontal N1 component revealed by Giard et al. (1990). The elicitation of the 40-Hz response may also subserve activation of frontal mechanisms, since N1 and the 40-Hz response show covariation across vigilance states (Tiitinen et al., 1994).

The MMN may also act as an attention trigger for widely deviant and obtrusive stimuli. Conscious perception of the stimulus could then possibly lead to the Orienting Response. Under conditions of low vigilance or at sleep onset, the N1 and the 40-Hz responses are reduced. The MMN is also reduced during NREM sleep. During REM sleep however, small amplitude N1 and MMN negativities may be present. The spontaneous 40-Hz response is also evident in REM. Thus some capacity for processing of deviant (and thus relevant) stimuli may persist. This function would be carried out by the computational neurons of the supratemporal component of the MMN which remain active in REM sleep. This capacity may be attributed to the high level of cortical arousal associated with the REM state. Thus a small amplitude MMN is elicited in REM sleep. On the other hand, because of the decreased cortical activation in REM, relative to the waking state, the computational neurons of the supratemporal MMN may not be sufficiently stimulated to activate the frontal

component of the MMN. In the same way, auditory stimuli do not "re-set" the 40-Hz response in REM because this information does not reach frontal centres associated with conscious awareness of the stimulus.

Conclusions

The conclusions of the present series of studies are as follows:

1. The MMN is elicited in waking ignore (reading) conditions to large and small deviations in auditory frequency, increments and decrements in stimulus duration, and increments in stimulus intensity.
2. The MMN is elicited in REM sleep to large and small deviations in auditory stimulus frequency.
3. The MMN in REM sleep to large frequency deviations is reduced in amplitude relative to that in wakefulness. The MMN to small frequency deviations is not.
4. Small amplitude negativities are elicited in REM sleep to increments and decrements in stimulus duration that conform to the latency and scalp distribution of the MMNs elicited by the same stimuli in wakefulness.
5. The MMN is not elicited in REM sleep by deviant intensity increments or decrements.
6. Deviant intensity increments elicit late negativities in REM and Stage 2 sleep that conform to the latency and scalp distribution of N350.
7. The MMN could not be elicited in NREM sleep by any type of deviant stimulus.

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Appendix A: The Effects of Digital Filtering on the Detection of the Mismatch Negativity in Slow Wave Sleep

Abstract

The mismatch negativity (MMN) is a slow frequency event-related potential (ERP) elicited when a subject is presented with a deviant auditory stimulus presented in a train of homogeneous background stimuli. The MMN has yet to be recorded in slow wave sleep (SWS). This may be because it is overlapped in time and space by slow frequency, high amplitude delta waves. Optimal filtering may however attenuate this background EEG. Different high and low pass digital filters operating in the frequency domain were applied to waking and sleeping MMN data obtained from four subjects. The results indicate that a bandpass of 3 to 12 Hz provided the best compromise for observing a possible MMN in SWS without a corresponding loss in the amplitude of the waking MMN. Despite the use of this optimal filtering condition, polarity inversion at the mastoid, typical of the MMN, was not observed during SWS.

Introduction

When a subject is presented with a deviant stimulus occurring in a train of repetitive identical (or "standard") stimuli, a "mismatch negativity" (MMN) is elicited. The MMN is a small amplitude negative wave beginning about 100 ms and lasting up to 250 ms after stimulus onset. The results of early studies indicated that the MMN occurred automatically and was independent of attentional state (Näätänen et al., 1978; Sams et al., 1985). Recent evidence suggests that in some instances the MMN may be modulated by attention (Näätänen et al., 1993; Trejo et al., 1995; Woldorff et al., 1991).

Some laboratories have attempted to record the MMN during states of consciousness such as sleep. Although the MMN has been reported to occur during REM sleep (Campbell et al., 1992) or in association with the K-complex during stage 2 sleep (Sallinen et al., 1994), it has yet to be recorded during the deeper, non-REM sleep stages of 3 and 4, collectively known as slow wave sleep (SWS). One factor that may contribute to this is the signal-to-noise ratio. The tonic (or background) EEG during SWS is characterized by large amplitude slow waves ranging up to 400 μV while the amplitude of the MMN is very small (perhaps less than 1 μV during sleep). A method to reduce the amplitude of the background EEG is the use of filtering. Optimal high- and low-pass filters selectively attenuate frequency components below and above a range of interest while leaving the signal (the evoked potential) unaltered. In the case of the MMN in SWS, this ideal may be difficult to attain since the spectra of both will contain low frequencies. The purpose of the present study is to determine the optimal high pass filter for recording the MMN during SWS.

Methods

Data were collected from four young female adults (aged 19-21 years, mean=20) who spent one night in the sleep laboratory. Informed, written consent was obtained from all subjects prior to the study. Grass gold-cup electrodes were used to record EEG from midline frontal (Fz), central (Cz) , and parietal (Pz) sites. In addition, electrodes were placed at three equidistant points along a line extending from Fz down to and including the left mastoid. These were labelled L1, L2, and L3. The reference was the tip of the nose. A single channel of EOG was also recorded by referencing an electrode placed one centimetre above the outer canthus of one eye to another placed one centimetre below the outer canthus of the other eye. Electrode impedances were below 2 kOhms. The EEG and EOG signals were recorded with analog high- and low-pass filters set at 0.3 and 35 Hz (3 dB attenuation of power) respectively. Single trials were stored on-line for later off-line averaging. A 12-bit A/D converter was used to sample the physiological signals beginning 50 ms before stimulus onset and continuing for 500 ms following it. A total of 256 data points were sampled (i.e., the dwell time was 2.15 ms).

An auditory oddball condition consisting of 1000 Hz "standard" and 2000 Hz "deviant" pure tones was used to elicit ERPs. Stimuli were 50 ms tone bursts (rise/fall time = 5 ms) with an intensity of 80 dB SPL, presented with an inter-stimulus interval (ISI) of 600 ms. Stimuli were presented randomly with a probability of 0.8 for standards and 0.2 for deviants. Tones were presented in blocks consisting of 500 trials each. ERP data were recorded while the subjects read in bed prior to "lights out" and during subsequent SWS.

SWS (sleep stages 3 & 4) was identified at the Cz lead in accordance with the criteria of Rechtschaffen and Kales (1968). Stimulus presentation was initiated approximately five minutes into any episode of SWS. Single trial evoked responses in which the EEG exceeded +/- 200 μV or the EOG exceeded +/- 150 μV were removed on-line. Sleep trials associated with EEG arousals greater than five seconds in duration were later excluded from the analysis.

Averages of the standard and deviant stimulus presentations were then digitally filtered in the frequency domain using a technique developed by Yuen and Fraser (1979). Frequency domain digital filters have the advantage that they will not produce phase distortion sometimes observed with the computationally less sophisticated time domain filters (Cook & Miller, 1992). ERPs were fast Fourier transformed (FFT) to the frequency domain and thereafter multiplied with a transfer function. The roll-off of the stop-bands was defined by half a cosine function. In order to prevent box-car filter shapes, the original ERPs were padded with zeroes to increase resolution. Finally, the filtered ERPs in the frequency domain were inversely transformed (i.e., the inverse of the FFT) to the time domain.

Five different high-pass filters were employed (low-pass 12.0 Hz), each having a 3 dB attenuation in power (the 12 dB setting appearing in parentheses determined the steepness of the roll-off): 0.3 (0.1), 1.0 (0.8), 2.0 (1.8), 3.0 (2.8), and 4.0 (3.8) Hz. Four different low-pass filters were used (high-pass 0.3 Hz), again with a 3 dB attenuation and the steepness of the roll-off determined by the 12 dB setting (in parentheses): 35 (40), 24 (27), 12 (14), and 6 (8) Hz.

Results and Discussion

The effects of varying the low-pass on the standard, deviant, and difference (deviant - standard) grand averages for both the awake and stage 4 conditions, as measured at Cz, are presented in Figure 1. In this figure, the high-pass filter was set at a constant 0.3 Hz. The top tracings (lo pass=35 Hz) represent the unfiltered data. In the waking grand averages, the 2000 Hz deviant tones are associated with a greater negativity than the 1000 Hz standards. This is evident in the difference waveforms where a clear MMN appears between 100 and 150 ms. In contrast, the grand average ERPs in SWS are characterized by a predominant slow positivity which is larger for the deviant tones. This results in a difference consisting of a large positive wave lasting throughout the typical MMN latency range of approximately 100 to 300 ms. Superimposed on this positive wave however, is a small negative peak at approximately 200 ms. It is possible that this 200 ms negative peak in SWS represents a longer latency MMN that is being "pulled down" by the large slow positive wave. As the low-pass filter is changed from 35 to 6 Hz, there is a gradual "smoothing" of the waveforms due to the attenuation of higher frequencies. As one would expect, this is more pronounced in the awake condition because of the higher frequency activity which typifies waking EEG. It is only when the most extreme 6 Hz low-pass filter is used that MMN morphology is markedly affected.

INSERT FIG. 1 ABOUT HERE

The effects of applying the high-pass filter are illustrated in Figure 2. In this case, the low-pass filter setting was held constant at 12 Hz because that setting provided the smoothest MMN (i.e., attenuation of unwanted high frequencies) without a concomitant loss in signal amplitude. During wakefulness, varying the high-pass filter from 0.3 to 2.0 Hz had a minimal effect on the appearance of the MMN. The 4.0 Hz high-pass filter resulted in a marked decrease in MMN amplitude, whereas the 3.0 Hz filter produced only a slight attenuation. During SWS, the gradual removal of slow frequencies caused the negative-going peak at approximately 200 ms to approach baseline.

INSERT FIG. 2 ABOUT HERE

Achieving a satisfactory signal-to-noise ratio is an important concern when attempting to record the MMN from sleeping subjects. This will be difficult due to the relatively small magnitude of the MMN response embedded in a background consisting of slow waves. Even following signal averaging procedures, a large amount of background noise may remain. One way of overcoming this problem is to present considerably more deviant trials. This is not always feasible because of the limited duration of SWS. An alternative is to filter the ERPs in order to attenuate unwanted frequencies. Some compromise will however be required since the frequency spectra of the MMN partially overlaps the background delta activity. Low-pass filtering down to 12 Hz had a minimal impact on the waking or sleeping MMN. Since 12 to 14 Hz spindle activity is present during SWS, a sharp 12 Hz filter (such as the one used in the present study) would markedly attenuate this activity. In contrast, the

selection of the high-pass filter may have a significant impact on the appearance of the MMN. Increasing the high-pass setting will significantly attenuate overlapping delta activity. A 4.0 Hz filter may effectively remove most of the delta activity during SWS and thus permit the visualization of the MMN. Unfortunately it also markedly attenuates the amplitude of the waking MMN. A reasonable compromise might therefore be a 3.0 Hz filter. This has only a slight effect on the MMN when the subject is awake but still excludes most of the unwanted delta activity when the subject enters SWS.

The intent of the present paper was to determine the effects of digital filtering on the MMN. Because of the small sample size, a definitive answer to the question of whether the MMN can be recorded during SWS remains tentative. A possible MMN candidate peaking at about 200 ms was observed at the fronto-central electrode The MMN should however invert in polarity at the mastoid when a nose reference is used (Alho et al., 1986). As is apparent in Figure 3, there is little evidence of this inversion. It is doubtful therefore that the small fronto-central negativity is a true MMN.

INSERT FIG. 3 ABOUT HERE

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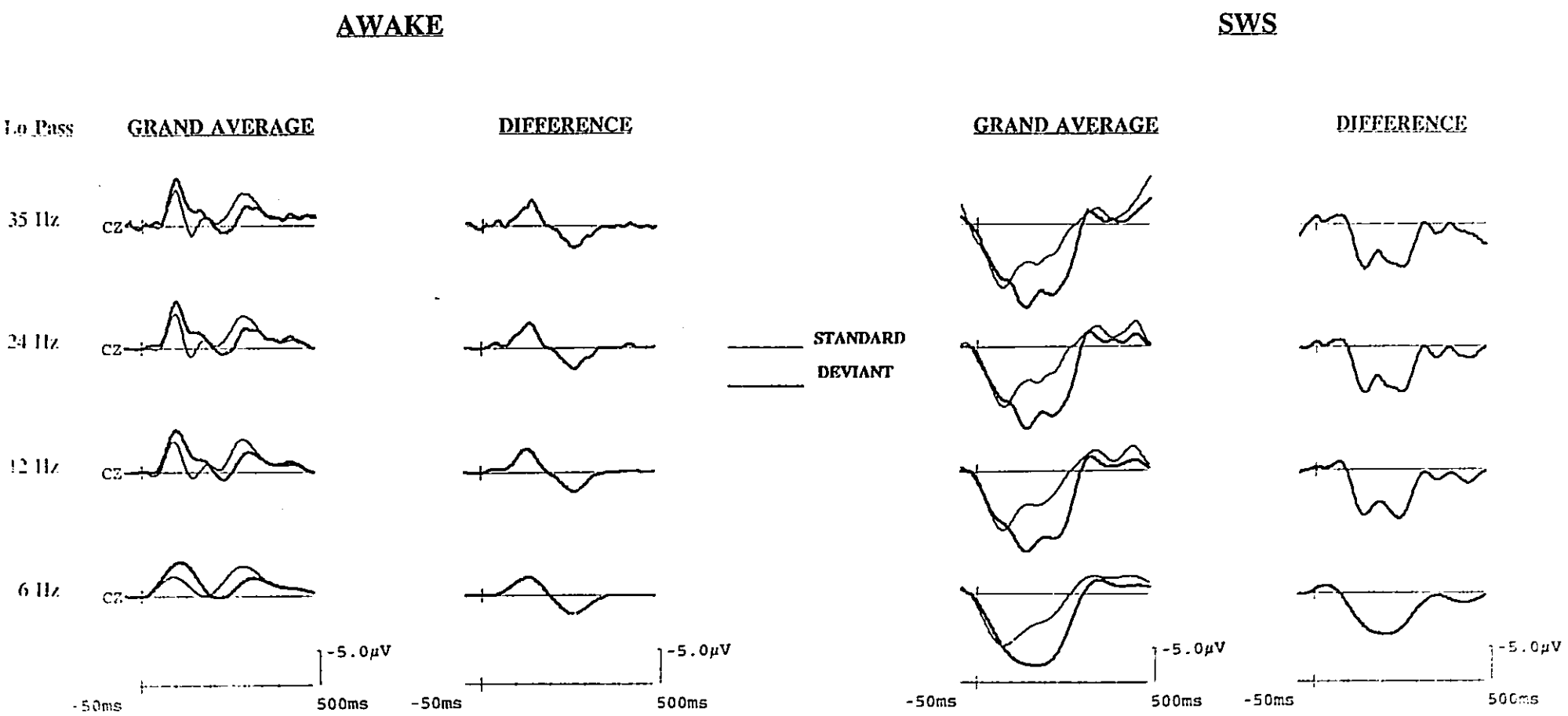
Figure Legends

Figure 1. Low-pass filter effects on standard, deviant, and difference (deviant-standard) grand averages. High-pass filter set at 0.3 Hz.

Figure 2. High-pass filter effects on standard, deviant, and difference (deviant-standard) grand averages. Low-pass filter set at 12 Hz.

Figure 3. Standard, deviant, and difference (deviant-standard) grand averages for all electrode sites filtered with a bandpass of 3 to 12 Hz.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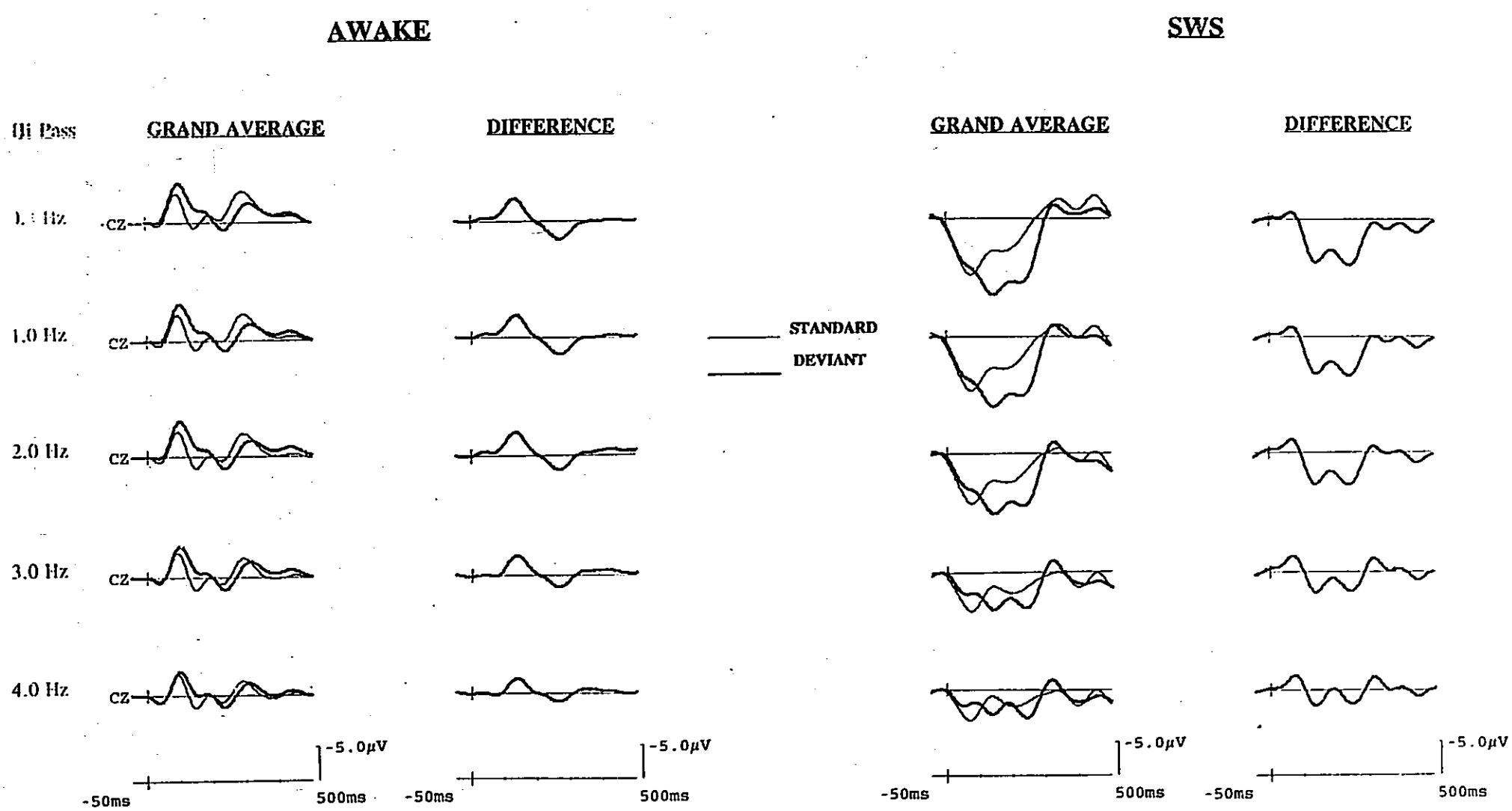
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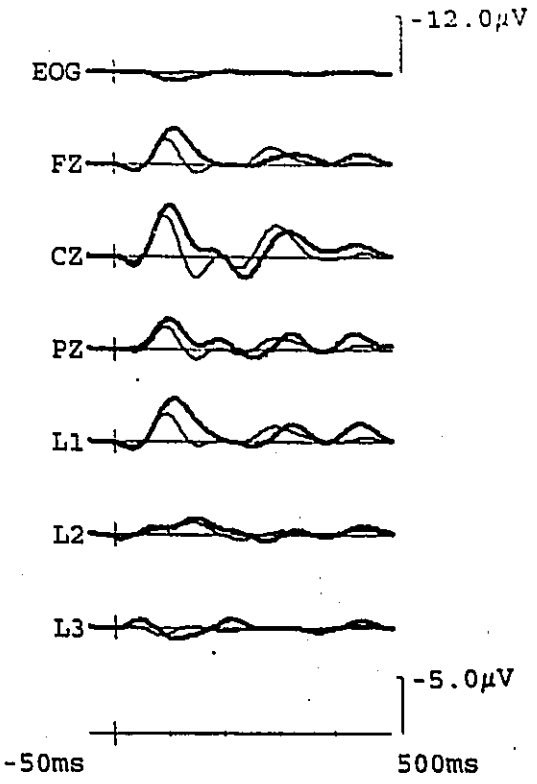
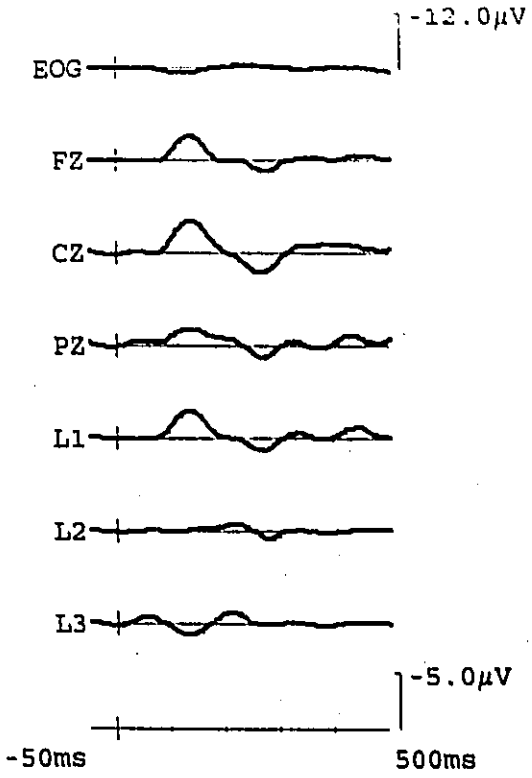
DIFFERENCE

AWAKE





STANDARD

DEVIANT

SWS