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Event-Related Potential Measures of Stimulus Change Detection During Wakefulness and Sleep Onset

by

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Abstract

The Mismatch Negativity (MMN), an auditory event-related potential (ERPs) reflecting the detection of stimulus change, was recorded during wakefulness and sleep onset. In Experiment 1, a 1000 Hz standard stimulus was presented every 600 ms. On 20% of the trials, the standard was changed randomly to either a large 2000 Hz (p=.10) or a small 1100 Hz (p=.10) deviant. During alert wakefulness (reading a book), a long-lasting MMN was elicited by presentation of both the small and the large deviant. During relaxed wakefulness (when the subject was asked to fall asleep) and Stage 2 sleep, the MMN to the large deviant, albeit attenuated, remained statistically significant.

To test the hypothesis that sensory memory fades rapidly during sleep, Experiment 3 employed a very rapid rate of stimulus presentation. Experiment 2 was used to identify the optimal stimulus parameters for that test by examining the interactive effects of stimulus probability and stimulus presentation rate on the MMN during wakefulness. Auditory stimuli were 1000 Hz standard and 1100 Hz deviant. Stimulus probability was varied across stimulus-onset asynchronies (SOAs) of 150, 600, and 2400 ms. A long-lasting MMN was evident in all conditions except at the longest SOA (2400 ms). When the SOA was 150 ms, the largest MMN was elicited to the lowest deviant probability.

In Experiment 3, a long-lasting MMN was elicited in alert wakefulness to either a small deviation (1100 Hz, p=.033) or a large deviation (2000 Hz, p=.033) from the standard (1000 Hz) in auditory frequency. SOA was 150 ms. A long-lasting MMN to the large deviant was observed during relaxed wakefulness, Stage 1 sleep, and non-REM sleep.

The results of these experiments support the hypothesis that the MMN comparison system is at least partially automatic. It can be elicited during non-REM sleep, at least to large

deviations in auditory frequency. The MMN following a small deviant is, however, difficult to observe during Stage 1 sleep or even as soon as relaxed wakefulness. It is possible that, during sleep onset, cortical encoding of both standard and deviant stimuli is weakened because of prior thalamic inhibition of sensory input.

To R. S., M. L., & R. J. M.

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Curriculum Studorium

Merav Sabri was born in Tel Aviv. Israel on October 20th. 1969. She pursued a Bachelor degree in Psychology and Education at the Open University and graduated Magna Cum Laude in 1995. She then completed her Master degree in Experimental Psychology Magna Cum Laude in 1998. Her graduate studies were supported by University of Ottawa. International and Admission Scholarship. During her academic training. she published a series of journal articles and abstracts. and presented papers at various scientific meetings.

Publications

Articles Published or Accepted in Referred Journals

Sabri. M.. & Campbell. K. B. (in press). Effects of sequential and temporal probability of deviant occurrence on mismatch negativity. *Cognitive Brain Research.*

Sabri. M.. Melara. R. D.. & Algom. D. (2001). A confluence of contexts: Asymmetric versus global failures of selective attention to Stroop dimensions. *Journal of Experimental Psychology: Human Perception and Performance. 27.* 515-537.

Sabri. M.. de Lugt. D. R.. & Campbell. K. B. (2000). The Mismatch negativity to frequency deviants during the transition from wakefulness to sleep. *Canadian Journal of Experimental Psychology. 54.* 230-242.

Sabri. M.. & Campbell. K. B. (2000). Mismatch negativity to inclusions and omissions of stimulus features. *NeuroReport. 11.* 1503-1507.

Articles Submitted for Publication (or in preparation)

Sabri. M.. & Campbell. K. B. The effects of digital filtering on mismatch negativity. Submitted.

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Conference Presentations

Sabri, M., Labelle, S., & Campbell, K. B. Effects of loss of consciousness on the MMN using a rapid rate of presentation. Poster to be presented at the 41st Annual Meeting of the Society for Psychophysiological Research (SPR), October 2000, Montreal, Quebec, Canada.

Melara, R. D., & Sabri, M. A confluence of contexts: Asymmetric versus global failures of selective attention to Stroop dimensions. Spoken paper presented at the Psychonomic Society 41st Annual Meeting, November 2000, New Orleans, Louisiana, USA.

Sabri, M., & Campbell, K. B. Effects of sequential and temporal probability on mismatch negativity. Poster presented at the 40th Annual Meeting of the Society for Psychophysiological Research (SPR), October 2000, San Diego, California, USA.

Sabri, M., & Melara, R. D. ERP effects of attentional training and stimulus congruity in the Stroop task. Poster presented at the 39th Annual Meeting of the Society for Psychophysiological Research (SPR), October 2000, Granada, Spain.

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Organizational Note

This dissertation consists of five chapters. Chapter 1 is an introduction to and review of the relevant literature and presents the rationale for the series of studies which follow. Chapters 2 through 4 represent the three experiments conducted for the doctoral dissertation. They are presented in journal article format and as such the style conforms to the publication requirements of the journal to which it has been submitted. Each chapter contains a separate Abstract, Introduction, Methods, Results, and Discussion section. A complete reference list is provided at the end of the thesis. Chapter 3 is followed by a separate reference list. This list is provided because the references in text are identified using a number system, rather than by author's name and year of publication. The fifth and final chapter provides a general discussion which integrates the three experiments, summarizes findings, and discusses their implications. Appendix A represents an article published during the doctoral program which is outside the focus of the thesis.

Chapter 2 has been published in *Canadian Journal of Experimental Psychology*, 2000, *54*, 230-242. Chapter 3 is "in press" in the Journal *Cognitive Brain Research*. Chapter 4 has been submitted to the journal *Psychophysiology*. Appendix A has been published in the journal *NeuroReport*, 2000, *11*, 1503-1507. M. Sabri is senior author on all publications. Data for Experiment 1 were analyzed from the Psychophysiology Laboratory archives. Otherwise, M. Sabri was responsible for all data collection, analysis, and write-up. The sleep data was scored by experienced polysomnographic technologists according to the criteria of Rechtschaffen and Kales (1968). The design and write-up of the various experiments was discussed with the thesis supervisor.

Chapter 1

Introduction

Change is ubiquitous. A stimulus array normally varies continuously across both time and space. Sounds change in auditory frequency, timbre, intensity, tempo, and location. Sights change in spatial frequency, hue, saturation, brightness, and location. The human central nervous system is exquisitely poised to detect and process these environmental variations using, in part, cortical modules dedicated to specific sensory dimensions of change (Zeki, 1993). Indeed, perception is impossible without change because all sensory channels require a certain level of stimulus variation to maintain perception. For example, an image stabilized on the retina, which produces constant stimulation to visual receptors, degrades and disappears from conscious perception (Cornsweet, 1969; Pritchard, Heron, & Hebb, 1960). A homogenous visual field (a Ganzfeld) creates a disoriented field of viewing and a breakdown in color quality (Cohen, 1958; Hochberg, Triebel, & Seaman, 1951). Change is a necessary prerequisite for veridical perception.

The evolutionary advantages of the ability to detect environmental change are obvious. To be successful in hunting prey or avoiding predators our hominid ancestors required the skill to notice variation in visual, tactile, olfactory, and auditory scenes. The sound of a broken twig, a shift in terrestrial vegetation during travel, a sweet-scented odor wafting newly in the air -- the facility with which our ancestors could detect the deviant sensory stimulation surrounding them determined how frequently they ate and how well they avoided being eaten, behaviors which led to more successful (or unsuccessful) strategies of reproduction.

A History of Behavioral Research on Change Detection

The present dissertation is an investigation of the neural processes of change detection. A specific electrophysiological response, called the Mismatch Negativity or MMN, has been identified as a primitive mechanism for noticing change in the acoustic environment. The MMN is thought to be independent of attention or, indeed, of even conscious awareness. The thesis evaluates this assumption by examining whether the MMN response is evoked during a prototypical state of unconsciousness, namely, sleep. To place the current study in perspective, previous research on the nature of change detection will be reviewed first. The bulk of prior research has been conducted using behavioral methodologies. The results of these behavioral studies have led to several fundamental insights about the theoretical basis of change detection.

Classical Psychophysics

From its inception, the discipline of psychology has focused empirical and theoretical investigations on human change detection. In his classic text, *Elements of Psychophysics*, Gustav Fechner (1860/1966) introduced a set of behavioral paradigms that has enabled several generations of subsequent researchers to determine human thresholds for detecting sensory change. Methods for measuring absolute threshold -- including the method of limits, the method of constant stimuli, and the method of adjustment -- are concerned with how well a perceiver can detect the *presence* of sensory stimulation. The ability to detect stimulus *change* was measured more directly when assessing the difference threshold, which is also called the just noticeable difference (jnd): the smallest difference between two stimuli that an individual can just consciously detect.

Just Noticeable Difference. To determine the difference threshold, psychophysicists present the observer with two stimuli: a standard stimulus and a deviant or comparison stimulus. For example, the stimuli may be two sounds of the same intensity, timbre, and location that differ in auditory frequency. The standard stimulus might be 1000 Hz and the deviant stimulus might be 1004 Hz. On each trial, the two sounds are presented in pairs, randomly ordered, one sound at a time. The observer is asked to decide whether the sounds on each trial are the same or different. If the comparison sound of 1004 Hz was distinguished accurately from the standard sound on 75% of the trials, then the difference threshold is 4 Hz (1004 Hz - 1000 Hz). In other words, in the 1-kHz range, the just-noticeable difference or jnd is 4 Hz. Ernst Weber (1846) discovered that the jnd varies in constant proportion (K) to the size of the standard stimulus. Fechner expressed this relation in Weber's law: jnd/Standard = K.

For our purposes, the importance of Fechner's jnd lies in it representing the first scientifically plausible attempt to scale psychological change. Thus, the concept of the jnd was, in essence, the first measure of change detection. Importantly, Fechner, and later psychophysicists in the classical tradition, believed that (1) the jnd is *absolute* -- it remains the same, in principle, whenever it is measured -- and (2) the jnd unit is psychologically *constant* -- it reflects basically the same psychological experience wherever on the scale it is measured.

Thurstone's Law of Comparative Judgment

Fechner's model of stimulus change, the jnd, was challenged in 1927 when Louis Thurstone detailed an entirely different approach to the measure of psychological experiences. The target of Thurstone's challenge was Fechner's idea that the jnd unit was a fixed entity. Thurstone pointed out that in tasks requiring a comparison between standard and deviant stimuli,

identical pairs will often lead to different responses across trials. Thurstone was convinced that such "aberrations" (from Fechner's point of view, at least) could conceivably reflect a lawful process of change detection.

Discriminal Processes. On Thurstone's view, presenting an observer with a stimulus activates one value along a psychological continuum. Presenting another stimulus creates a "discriminal process" to the first stimulus, even if the two stimuli are physically identical. Thus, the different discriminal processes create a distribution of values along the psychological continuum, which Thurstone believed was Gaussian in form. When a stimulus is presented, therefore, the probability that a particular value is activated corresponds to expectations derived from the normal distribution. The psychological value most likely to be experienced corresponds to the mode of this distribution, or what Thurstone called the "modal discriminal process." The difference between the mode and some other value from the normal distribution was called the "discriminal dispersion." This difference corresponds to the standard deviation of the normal distribution.

Discriminal Differences. Thurstone's *Law of Comparative Judgment* was based on the "discriminal differences" that result when observers compare one stimulus with another. If an observer is asked to judge the higher pitched of two sounds, x and y, each sound will give rise to a discriminal process along a psychological scale, x and y, respectively. Because x and y are normal deviates (i.e., they correspond to values sampled from a normal distribution), they vary from trial to trial in accord with Gaussian probability. The difference between x and y on any given trial is the discriminal difference. Across many trials, a distribution of discriminal differences is formed, which has a mean of z, corresponding mathematically to Fechner's jnd.

Thurstone's law is important historically because it represents the first time change detection was conceived as being fundamentally probabilistic. In contrast to Fechner, who viewed change detection as a fixed process, Thurstone believed that the process was inherently noisy. He maintained that the variability in judgments that classical psychophysicists attributed to measurement error was actually an intrinsic part of the judgment process. The full impact of Thurstone's ideas were only realized several decades later, however, with the development of the theory of signal detection (Green & Swets, 1966).

Signal Detection Theory

Thurstone's idea that physical stimulation creates a distribution of effects along a sensory continuum was expanded upon in the 1950's by engineers in the United States, at the University of Michigan and the Massachusetts Institute of Technology (MIT), and in the Soviet Union (see Macmillan & Creelman, 1991), although all of them were probably unaware of Thurstone's work. These engineers were concerned with the detection of radar and sonar signals amid the noise that is intrinsic to the signal itself. One can represent a signal and the surrounding noise stochastically by a distribution of effects, as in Thurstone's conception. Of course, the signal distribution might partially overlap with the noise distribution along the psychological scale. The engineers were thus faced with describing how radar or sonar technicians discriminate between a random value that conceivably might arise from either of the two distributions: (a) a distribution of the noise and (b) a distribution of a signal added to the noise (signal + noise). As we shall see, the answer to their problem came from statistical decision theory.

Two Mechanisms of Change Detection. The ideas developed by these engineers were borrowed by psychologists Tanner and Swets at the University of Michigan, and used to

formalize what psychologists now call *signal detection theory* (see Green & Swets, 1966). The theory represents a radically new approach to the study of change detection. Rather than assuming that the perception of stimulus presence (absolute) or change (difference) is limited by fixed thresholds of the sensory system. Tanner and Swets proposed that behavioral responses to stimuli originate in two independent mechanisms: (1) the inherent *sensitivity* of the observer's sensory system and (2) circumstantial *biases* influencing how the observer reaches decisions about the stimuli. Consider again an observer who is presented with pairs of sounds, one standard and one comparison in random order. Suppose at first that the observer's rate of correct discriminations (i.e., saying "different" when the sounds actually differed) was only 50% (i.e., chance performance). We might conclude that the physical difference between stimuli falls below the observer's inherent difference threshold. But suppose we perform the task again, this time rewarding the observer with $30 for each correct response. If accuracy now jumps to 75%, a classical psychophysicist would have difficulty explaining why, because the difference threshold should remain fixed. According to signal detection theory, the sensitivity of detection may be fixed, but motivational biases in responding can change depending on circumstances.

A Signal Detection Experiment. In a typical signal detection experiment, each trial contains only one stimulus, either the standard (noise) or the deviant (signal + noise). (Hereafter, when the term "signal" is used alone it refers to a signal superimposed on background noise.) The stimuli are presented randomly. Often, the probability of presentation differs between the two stimuli. For example, the standard may be presented on 85% of the trials, whereas the deviant is presented on only 15% of the trials. The observer is being asked to respond "yes" each time he or she detects a deviant signal and "no" otherwise. Four different response patterns are possible. A "hit" refers to the probability that the observer responded "yes" when the deviant

signal was actually presented: P("yes"|Signal). A "false alarm" refers to the probability that the observer responded "yes" when no signal was presented (that is, when the standard stimulus was presented): P("yes"|Noise). A "miss" refers to the probability that the observer responded "no" to the deviant signal: P("no"|Signal). A "correct rejection" refers to the probability that the observer correctly responded "no" to the standard: P("no"|Noise).

The sensitivity of an observer can be expressed as d', defined as the z-transformed hit rate minus the z-transformed false-alarm rate: d' = z(hits)-z(false alarms). The response bias of an observer can be expressed as the criterion or c, defined as half the sum of the z-transformed hits and false alarms: c = .5[z(hits)+z(false alarms)] (see Macmillan & Creelman, 1991). The likelihood ratio at the criterion is expressed as β. For reasons of simplicity, the criterion c will be used throughout.

Sensitivity. According to the signal detection theory, each presentation of a signal (deviant) or noise (standard) activates a mental representation in the sensory system. The level of activation of this representation describes a sensory continuum. Importantly, activation is assumed to be stochastic (probabilistic), not deterministic. Thus, the exact same physical stimulus presented on two occasions may not yield the same level of activation along the sensory axis. To characterize the stochastic process, signal detection theorists borrowed the perceptual theory proposed earlier by Thurstone (1927): For a given stimulus (e.g., 1000 Hz tone), the probability distribution of perceptual effects along the sensory continuum elicited by repeated presentations is presumed to be Gaussian in form. Thus, the signal stimulus and the noise stimulus can each be described by their own normal probability distributions. The more perceptually similar the two stimuli, the greater the overlap of these distributions along the

sensory axis. Sensitivity or d' is defined theoretically as the difference between means of the two probability distributions divided by their pooled standard deviations.

Decision Processes. The greater the overlap between the signal and noise distributions, the more difficulty an observer experiences in reaching a decision about the identity of a stimulus on any given trial. To deal with the uncertainty in decision making, signal detection theorists proposed that the observer erects a decision boundary or criterion along the sensory axis (Ashby & Townsend, 1986). A perceptual effect is then categorized as "signal" or "noise" on each trial depending on the level of activation with respect to the criterion. In the actual experiment, then, the observer will respond (that a deviant signal has been presented) only when the magnitude of the perceptual effect exceeds the criterion. The contribution of signal detection theory, therefore, lies in its incorporation of statistical decision processes into the mechanisms of detecting stimulus change.

The decision criterion can take several forms. When c equals zero, the decision boundary is said to be unbiased. This occurs when the false alarm rate equals the miss rate. If the variances in the two probability distributions are equal, the unbiased criterion is optimal for maximizing hits and minimizing false alarms. Two types of biases, however, also can guide decision making. A negative criterion means that the observer is biased in favor of responding (i.e., a liberal bias: saying "yes" whether or not a signal appears): a liberal bias can be created when the observer is rewarded for hits, but not penalized for false alarms (i.e., the false-alarm rate exceeds the miss rate). A positive criterion means that the observer is biased in favor of not responding (i.e., a conservative bias): a conservative bias can be created when the observer is penalized for false alarms (i.e., the miss rate exceeds the false-alarm rate). In each of these cases, the detection of change is directed by strategic decisional processes. Importantly,

although the criterion may vary across the different conditions, the observer's sensitivity d' will remain constant. Thus, for a constant level of sensitivity, a plot of false-alarm rates against hit rates in the different conditions (i.e., at the different levels of the criterion) creates a single ROC (receiver-operating characteristic) curve in discrimination space.

Sensory Memory

The goal of the ideal observer in a signal-detection experiment is to identify correctly as many occurrences of the deviant signal as possible, without falsely responding to the standard (noise). One approach for performing signal detection is mentally to compare the stimulus on the current trial with the memory of stimuli on preceding trials. For example, if the last trial is known to have contained the standard stimulus, then any perceptual difference noticed between the memory of that stimulus and the experience of the current stimulus prompts the observer to respond "yes" on the current trial. This approach becomes the optimal one the greater the probability of presentation of the standard relative to the deviant. With repeated presentations of the standard, recurrent perceptual activation of the stimulus representation creates a brief sensory memory trace which can serve as one basis of discrimination. The trace is disrupted by stimulus change, which signals the detection of the deviant stimulus.

Iconic Memory. Research on sensory memory began with the seminal studies of George Sperling (1960). In his Ph.D. dissertation, Sperling developed the method of partial report: Observers were presented briefly (50 ms) with a 3 x 4 array of letters and numbers. The observers were unable to report more than about four items from the 12-item array at one time (whole report). Nonetheless, inspired by his subjects' claims that they could "see" more than four items, Sperling believed that a short-duration sensory memory of the entire array was stored

internally, but that the act of whole report exceeded its duration. He reasoned that by cuing observers to one of the three rows of the array after its presentation he could investigate the hypothesized sensory-retention mechanism. Indeed, Sperling discovered that observers had perfect memory of the cued row if the cue (a tone) was presented within 500 ms of the array. With longer delays, subjects were unable to report the entire cued row perfectly.

Sperling concluded that subjects had a brief but detailed memory of the entire array, since they had no advance knowledge of which row would be cued. The memory is lost, he argued, if subjects do not attend to it quickly (within 500 ms). The memory was dubbed *iconic memory* (Neisser, 1967) to suggest a precise, but quickly-decaying picture in the mind. Iconic memory is assumed to be precategorical, meaning that it contained information in an unanalyzed form, although several experiments have questioned this claim (Haber, 1983; Merikle, 1980). Although Sperling suggested that the duration of iconic memory is several hundred milliseconds, more careful subsequent experiments have shown that visual persistence lasts no longer than 120 ms (Cowan, 1995; Di Lollo, 1980; Francis, 1996).

Echoic Memory. An analogous auditory sensory memory, dubbed *echoic memory* (Neisser, 1967), was discovered in later studies using a variety of techniques (Darwin, Turvey, & Crowder, 1972; Deatherage & Evans, 1969; Efron, 1970a, 1970b). Darwin et al. presented subjects with three lists of three digits, each list presented from a perceptually distinct spatial location. A visual signal cued the subject which list to report. As in the visual modality, an advantage for partial report (one list-three digits) over whole report (9 digits) was found. Unlike the visual modality, however, this advantage was observed for cue delays of up to 4 s, suggesting that echoic memory has a greater duration than iconic memory. The study by Darwin et al. has been criticized, however, for procedural confounds (Massaro & Loftus, 1996). An

unconfounded replication (Massaro, 1976) suggested that auditory sensory storage lasts no longer than 250 ms (see also Efron, 1970a; Massaro, 1972), placing it within the range of iconic memory. More recently, however, Cowan (1984, 1995) has proposed that two distinct auditory stores exist, one operating over a timescale of 150-350 ms, and the other lasting between 2 and 20 s. The longer store may underlie the so-called *modality effect*, the finding that the last few items on a list are remembered better if they are spoken (auditory) than read (visual) (Conrad & Hull, 1968; Crowder, 1970; but see Shand & Klima, 1981).

Automatic Processing

Research on iconic and echoic memory has underscored the passive nature of sensory storage. Subjects in Sperling's original study, for example, registered the entire stimulus array in memory merely by viewing it passively, in the absence of attention paid to the to-be-cued row. Cognitive psychologists use the term "automatic" to describe mental processes that neither require, nor are limited by, conscious attention. If the sensory memories that serve as the basis of deviance detection are registered and disrupted passively, perhaps the detection of stimulus change is an automatic process.

Criteria of Automaticity. Automatic processes are traditionally distinguished from controlled processes according to criteria set forth by Posner and Snyder (1975) and Shiffrin and Schneider (1977). Automatic processes are assumed to be fast, independent of processing strategies, and not reliant on attention for their execution. Performance on well-practiced tasks, such as reading for literate adults, might fall into this category. Controlled processes are assumed to be slow, voluntary, dependent on processing strategy, and requiring attention for

their execution. Performance on novel tasks, such as the naming of colors, might fall into this category.

The Stroop Task. A variety of different cognitive tasks have been employed to study the differences between automatic and controlled processes. Probably the most popular paradigm is the Stroop color-word task. Here a subject is asked to name the print color of color words (e.g., RED printed in green). The usual finding is that subjects are slow to perform this task, relative to naming the colors of colored squares. Conversely, subjects are no slower at reading colored color words (e.g., RED in green) than they are at reading uncolored color words (e.g., RED in black). The traditional *Stroop asymmetry* refers to this imbalance in selective attention performance: Words distract attention from color targets, but colors do not distract attention from word targets.

Stroop (1935) attributed the asymmetry in performance between color naming and word reading to differences in associative strengths, color naming being the relatively weaker skill because of the comparatively little training humans have had with this activity. In line with Stroop's account, modern theories most often explain the Stroop asymmetry by invoking the concept of automaticity (Hasher & Zacks, 1979; LaBerge & Samuels, 1974; Logan, 1980; Posner & Snyder, 1975): The extensive practice that literate adults have had in reading words has made this activity seem virtually effortless and involuntary (i.e., automatic), particularly when compared with color naming, which requires concentration and effort even for adults. Automaticity theories state, then, that the asymmetrically large influence of words on colors in the Stroop task arises from subjects' efforts to overcome their automatic tendencies to read and/or speak the words when attempting to name the colors.

Automaticy and Horse Race. In formal theories of the Stroop asymmetry (e.g., Cohen, Dunbar, & McClelland, 1990; Logan, 1980; Phaf, van der Heiden, & Hudson, 1990; Zhang, Zhang & Kornblum, 1999), the concept of automaticity figures into speed-of-processing or strength-of-processing architectures. Because of the automaticity bestowed by training, words are theorized to be processed intrinsically more efficiently than colors. On most trials of a Stroop task, analysis of the word is thought to be completed sooner than analysis of the color, and hence to have an earlier and stronger influence in decision making and response production (e.g., Dyer, 1973; Klein, 1964; Morton & Chambers, 1973; Posner & Snyder, 1975). One analogy is a horse race in which the word horse usually beats the color horse to the response finish line. Such speed-of-processing architectures can explain both the baseline differences Stroop (1935) found between word and color dimensions -- because the word horse finishes more quickly on average than the color horse -- and the Stroop asymmetry in selective attention -- because the fast word horse often disrupts decisions about the slow color horse, but not vice versa.

Partial Automaticity. Automaticity was conceived originally as an all-or-none phenomenon: A cognitive process was either automatic or controlled (see Cohen et al., 1990, for a review). Several researchers have begun to criticize this strong version of automaticity. Kahneman and Chajczyk (1983), for example, created a modified version of the Stroop task in which the color word appeared below a color patch. These authors found that when an additional word appeared in the display, the interfering effect on color naming of a conflicting color word was "diluted." It appeared that, by diverting their attention to the added word, subjects weakened the effect of the color word on color naming. This result suggests that attentional allocation might affect the automaticity of word reading, an idea contrary to the basic

criteria of automaticity. Kahneman and Chajczyk thus regarded their results as inconsistent with a strong version of automaticity and argued instead for the possibility of weak or partial automaticity. In line with their suggestion, others have argued that automaticity exists along a continuum: Extensive practice at a task enhances the automaticity of a process that might initially be controlled (Cohen et al., 1990; Logan, 1985; MacLeod & Dunbar, 1988; but see Logan, 1988).

Limitations of Behavioral Research

The concept of automaticity relies on the view that certain cognitive processes are not amenable to conscious awareness or attention. In this sense, the study of automatic processes using behavioral techniques is, by definition, indirect. In the Stroop task, for example, automatic processes of word reading are inferred from their indirect influence on the conscious activity of color naming. The actual extent of cognitive processing cannot be observed directly. Another major drawback to using strictly behavioral approaches when studying selection processes is that measurable responses to unattended stimuli are difficult to extract without distorting the task itself. For instance, asking observers to respond to the words in a Stroop task changes that dimension's status from unattended to attended.

Traditional behavioral paradigms used in the study of automaticity and change detection -- including dichotic listening (e.g., Moray & O'Brien, 1967; Treisman, 1960), speeded classification (e.g., Garner, 1974; Stroop, 1935), and visual search (e.g., Treisman & Gelade, 1980) -- are burdened by several undesirable qualities. First, as mentioned, in these paradigms the mechanisms of automaticity are inferred only indirectly from a distractor's behavioral effects on the speed and accuracy in classifying targets. A negative priming effect in Stroop

classification (i.e., responses to the target on the current trial are slowed by its match to the distractor on the previous trial; see Dalrymple-Alford & Budayr, 1966; Neill, 1977), for example, provides only indirect evidence that distractors cause the buildup of inhibitory activation (Engle, Conway, Tuholski, & Shisler, 1995; Houghton & Tipper, 1996), a conclusion that is open to various alternative interpretations (see Milliken, Joordens, Merikle, & Seiffert, 1998; Neill, Valdes, Terry, & Gorfein, 1992; Tipper & Cranston, 1985). Second, to evaluate the degree of automaticity in these paradigms, ordinarily it is necessary to vary the type or range of unattended stimuli, thereby changing the actual physical stimulus features from one condition to another. In research conducted in the Garner tradition (e.g., Garner, 1974, 1983; Pomerantz, 1986), for example, distractibility is manipulated by varying the discriminability of points along the irrelevant dimension, which requires that the physical values of distractors change from task to task (e.g., Melara & Mounts, 1994). Third, in conventional paradigms attended and unattended stimuli often appear jointly on each trial -- as, for example, in the widely-used flanker task (Eriksen & Eriksen, 1974) -- making it especially difficult to segregate the automatic processes from the controlled processes. Finally, by requiring overt responses to the detected stimuli, behavioral paradigms confound the sensitivity of change detection with biases in decision making.

Bioelectric Effects of Cognitive Processing

To overcome the limitations of behavioral research, the present dissertation explored mechanisms of change detection using electrophysiological techniques. This approach allows the recording of physiological responses to stimuli without conscious discrimination or the requirement of behavioral responding. Using these techniques, the effects of stimulus change

and automatic processes can be studied directly, rather than inferentially. Moreover, the electrophysiological approach allows separate measurements to be made of attended and unattended stimuli (and stimulus changes), which do not need to appear concurrently on a trial. Finally, in the absence of behavioral responding, it is possible to evaluate physiological indices of sensitivity to stimulus change, without consideration or confounding of response biases. In this section, electrophysiological recording technique will be reviewed. Particular emphasis will be placed on the study of automatic neural mechanisms of stimulus change.

The Electroencephalograph

Scientists have been measuring the brain's electrical activity for more than 70 years using the electroencephalograph (EEG) (Berger, 1929). The EEG became suitable for cognitive research when G. D. Dawson (1951) developed a method of averaging the EEG signal immediately following a stimulus, resulting in a time-locked, evoked cerebral activity. The evoked potential (EP) signal is embedded in the noise of spontaneous EEG. The background activity of the EEG is usually very high in amplitude relative to the small amplitude EP signal. Because the EEG is assumed to be random in nature, averaging over many trials will reduce its amplitude progressively toward approximately zero. The signal of interest, the EP, remains apparent because it is a constant response that is time-locked to the stimulus. The average of a constant is, of course, the constant. The number of trials required to produce a reliable signal that can be distinguished from the background EEG noise is dependent on the amplitude of the signal and the amplitude of the background EEG. The smaller the signal and the larger the EEG, the poorer the signal-to-noise ratio (S/N), and the greater the number of trials needed for averaging. Averaging will attenuate the background noise such that residual noise (i.e., standard

error of the average) is directly proportional to the root-mean-square value or standard deviation of the noise and inversely proportional to the square root of the number of trials in the average.

Event-Related Potentials

Traditionally, obligatory short-latency electric responses evoked by sensory stimulation were labeled EPs, whereas later components associated with complex psychological/cognitive processes were termed event-related potentials (ERPs). In recent years, however, this distinction has been blurred and EPs are also referred to as ERPs. Accordingly, ERPs are defined now as changes in electrical activity of the nervous system that are elicited by an external physical stimulus or an internal psychological event (Picton, Lins, & Scherg, 1995). The primary source of scalp-recorded ERPs is believed to be synchronous post-synaptic activation of hundreds of thousands of pyramidal cells. Brain tissue can produce an externally observable electrical potential only if the neurons within the tissue are non-radially symmetric, spatially aligned, and synchronously activated. Pyramidal cells, which make 70% of the neocortex, seem to have all these qualities (Nunez, 1981).

Components of ERP waveforms. An ERP waveform consists of a series of "components" (Donchin, Ritter, & McCallum, 1978), negative or positive deflections (Näätänen & Picton, 1987) each of which can be described by its polarity (in μV), latency (in ms), scalp distribution, and relation to task variables. There is no single, universally accepted definition of an ERP component. Donchin et al. (1978) defined component as "a source of *controlled*, observable variability....a component can be assumed to exist only if it has been shown to vary systematically as a function of some independent variable" (p. 354). Näätänen & 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 directly measured from the average waveform, the components contributing to these peaks can usually be inferred only from the results of the experimental manipulation" (p. 376). Both definitions are very similar in determining a component, but the latter limits the outcome of an experimental manipulation to a distinct generator process. In the present dissertation, the term "component" will be restricted to the definition put forth by Näätänen & Picton (1987).

ERP components also are traditionally classified as "exogenous" or "endogenous" (Sutton, Braren, Zubin, & John, 1965). Exogenous ERP components are determined primarily by the physical characteristics of the eliciting stimulus. A change in the physical qualities of a stimulus will cause an exogenous evoked potential to vary. They typically occur obligatorily shortly after stimulus onset, regardless of the subjects' level of attention or conscious awareness. By contrast, endogenous ERP components are independent of the physical nature of the stimulus. They occur later in time and are dependent on complex psychological processes such as attention/consciousness, memory, comparison, decision-making, and relevance of the stimulus to the subject. The distinction between exogenous and endogenous components is not always dichotomous. As Picton and Hillyard (1988) note, there is "a continuum between the early exogenous potentials and the late wholly endogenous potentials, with many of the intervening components subject to both external and internal influences" (p. 361).

ERP Effects of Auditory Stimulation. ERP components have been elicited in all modalities. The focus of the present dissertation will be on the late auditory components. Auditory EPs (AEPs) have been divided according to their peak latency into early (short-latency, occurring from 1-10 ms), middle (mid-latency, occurring from 10-50 ms), and late components

(long-latency, occurring from 50-800 ms) (Davis, 1976). The early ERP components, called brainstem auditory evoked potentials (BAEPs), are almost entirely exogenous, reflecting activation of the acoustic nerve and brainstem auditory structures (Jewett & Williston, 1971). They depend strongly on the characteristics of the sensory stimulus and are relatively insensitive to task demands or the attentional level of the subjects (Picton, Stapells, & Campbell, 1981). Indeed, they are unaltered by states of unconsciousness (Campbell & Bartoli, 1986, Jones, 1994; Thornton, 1991).

The mid-latency components are thought to be generated in thalamic and cortical auditory structures. They are largely determined by the physical parameters of the stimulus, but might also be susceptible to attentional manipulation (Hackley, Woldorff, & Hillyard, 1987; Woldorff, Hansen, & Hillyard, 1987; Woldorff & Hillyard, 1991). The thalamus is the major gateway for the flow of sensory inputs to the cerebral cortex (except olfactory input which projects directly to the paleocortex), playing the role of filter or gate by inhibiting unattended or irrelevant sensory information (Steriade, McCormick, & Sejnowski, 1993). Unfortunately, the mid-latency components are difficult to record. Their measurement is affected greatly by artifacts, especially those associated with middle ear muscle activity.

The late components are largely endogenous, reflecting activation of the association areas of the cerebral cortex (Picton, Hillyard, Krausz, & Galambos, 1974). Because of their sensitivity to the physical characteristics of the stimulus, as well as to stimulus relevance, task requirements, and the subject's psychological state (Donchin et al., 1978), the late ERP components potentially can be used as a direct index of cognitive processes.

Late Auditory ERP Components

A convenient system for labeling the late components employs a combination of the component's polarity (i.e., positive or negative) and its sequential numbering (or, alternatively, its peak latency). An early small amplitude positive wave peaks at about 50-75 ms after stimulus onset and is maximal over central areas of the scalp. Because it is the first main positive wave that is observed, it is often labeled, P1. However, because it also peaks at about 50 ms, it may be labeled, P50. P1 is followed by a well-documented negative-positive complex, N1-P2. N1 peaks at about 80-140 ms and P2 peaks from 180 to 230 ms. N1 and P2 are two separate deflections. Each is affected differently by experimental manipulation and each has a distinct scalp distribution (Näätänen & Picton, 1987).

Characteristics of the N1 Component. The N1 potential does not represent a unitary event as reflected in a single cerebral process but is rather the product of multiple, simultaneously active generators. The intracranial sources of N1 are thought to be located in the auditory cortex on the supratemporal plane, in the association cortex on the lateral temporal lobe, and perhaps in the frontal lobe (Giard, Perrin, Echallier, Thévenet, Froment, & Pernier, 1994; Näätänen & Picton, 1987; Scherg, Vajsar, & Picton, 1989). The N1 response is maximum at the fronto-central areas of the scalp and inverts in polarity at the mastoid site (the large bony region behind the ear). It is evoked by a relatively abrupt change in the level of energy impinging on the sensory receptors (Näätänen & Picton , 1987), such as that following the onset and offset of an auditory stimulus occurring at unexpected times (Davis, 1939).

Sustained homogenous stimuli do not elicit the N1 (Näätänen & Picton, 1987). The amplitude of N1 to a continuous sound increases after a discriminable change in an acoustic feature, such as a new frequency or an increase in intensity. The increase in N1 amplitude is

proportional to the magnitude of the change. However, when rapid rates of stimulus presentation are used, N1 amplitude decreases. Moreover, the removal of a feature from the sound (e.g., the exclusion of a frequency band or a decrease in intensity) does not elicit an increase in N1. Taken together, the effect of stimulus change on N1 amplitude appears to reflect a process of recovery from stimulus-specific refractoriness. Further, N1 amplitude presumably is unrelated to habituation processes, because dishabituation has never been demonstrated reliably (Näätänen & Picton, 1987; Näätänen & Winkler, 1999).

Manipulations of a psychological state, selective attention, often has a consistent effect on the amplitude of N1. When relatively fast rates of stimulus presentation are used, N1 amplitude is larger in response to attended stimuli than to unattended stimuli. In a now classic study, Hillyard, Hink, Schwent, and Picton (1973) were the first to demonstrate reliable evidence of selective attention effects on the ERP waveform in the N1 latency range. In a dichotic listening paradigm in which stimuli were presented at short interstimulus intervals (random 100-800 ms), these authors found that the amplitude of the N1 component was larger in response to stimuli presented to the attended ear than to stimuli presented to the unattended ear. This effect was interpreted as the selective tonic facilitation of attended input by an early stimulus selection mechanism operating on the physical features of the stimulus (i.e., stimulus-set; Broadbent, 1970).

Näätänen, Gaillard, and Mäntysalo (1978, 1980) argued that the enhancement of N1 from attention was due instead to an overlap with an independent endogenous component that they termed the processing negativity (PN). These authors hypothesized that, because N1 is affected by the physical qualities of the stimulus, it is primarily exogenous in nature. Manipulations of attention, they claimed, affect a different negative component, the PN. PN may, however,

overlap and summate with N1 giving the appearance that N1 is increasing in amplitude due to increased attention. They argued that short interstimulus interval used by Hillyard et al.'s (1973) study may have caused a heavy stimulus load that stimulated attention. Topographical studies later revealed that the effects of N1 enhancement (Hansen & Hillyard, 1980) were distinct from the exogenous effects on N1 from short (Woods & Clayworth, 1987) or long (Giard, Perrin, Pernier, & perronet, 1988) constant interstimulus intervals. Nonetheless, exogenous N1 overlaps temporally with the earliest effects of auditory attention (Hackley et al, 1987; Woldorff et al., 1987; Woldorff & Hillyard, 1991).

When a channel to be attended is clearly distinct from that to be ignored, the peak of PN will occur quite early because the to-be-ignored channel can be rejected from further processing at earlier stages. In contrast, when the two channels are quite similar, the to-be-ignored channel must receive extensive processing before it can be rejected as irrelevant. PN will be similar in the attended and ignored channels for a long latency period. The additional processing that the attended channel receives (as reflected in PN) will therefore not be apparent until after the peak of PN. Accordingly, PN may or may not overlap with N1.

Components Evoked by Stimulus Change. A later negative wave, N2, peaking between 200 and 300 ms often can be recorded using an "oddball" paradigm in which "deviant" stimuli occur infrequently in a sequence of otherwise repetitive, homogeneous "standard" stimuli (Näätänen et al., 1978). Näätänen, Simpson, and Loveless (1982) demonstrated that N2 is comprised of at least two subcomponents. The first, labeled N2a, represents the mismatch negativity (described in the next section). The second, labeled N2b, has a slightly longer latency and appears as a sharper negative peak superimposed on the descending N2a. The N2b component may be followed by a late positive component, P3a. The P3a is maximal over fronto-

central areas of the scalp and peaks between 250-350 ms. Sams, Paavilainen, Alho, and Näätänen (1985) noted that the N2b-P3a complex may be elicited for deviant stimuli that differ greatly from the standard stimuli in conditions in which subjects are instructed to ignore the stimuli. Although engaged in a primary task (e.g., reading), subjects can be distracted by and switch attention to a very discrepant deviant. The process reflected in the N2b-P3a complex thus provides a means by which subjects can become conscious of an ignored deviant stimulus. When subjects are asked consciously to detect the deviant stimulus actively, a later parietal positivity, the P3b (or "P300" since it occurs at about 300 ms) is elicited. There is very good evidence that P300 reflects conscious detection and classification of the rare deviant stimulus (Picton, 1992).

The Orienting Response. The N2 component has been suggested to play a role in the initiation of the orienting response (OR) by stimulus change (Näätänen & Michie, 1979). The OR was first illustrated by Pavlov in 1927 to describe a reflex that brings an immediate response to the slightest change in the environment. Pavlov noticed that dogs undergoing classical conditioning were interrupted whenever a new person or stimulus entered the laboratory as they oriented their eyes and ears toward it. A variety of physiological changes occur when an organism is presented with a novel stimulus (Lynn, 1966). These include pupil dilation, increased electromyogram (EMG) activity, increased frequency and lower amplitude EEG, increased amplitude and decreased frequency of respiration, slowing heart rate, and changes in electrodermal activity (EDA). Stimuli that bear the potential of eliciting the OR are novel, intense, colorful, meaningful, surprising, complex, incongruous, and conflictual (Berlyne, 1960).

Based on Sokolov (1963), it has been a common assumption that the OR is the outcome of a comparator mechanism in which stimulus input is matched with memory representations. If

a stimulus is novel and does not match any of the existing neuronal models, a "nonsignal" OR will occur. On the other hand, if a stimulus does match an element in memory that is meaningful to the organism, a "signal" OR will be elicited.

Öhman (1979) proposed an information processing model of the OR that combines Sokolov's ideas with constructs derived from contemporary work in attention and memory. An OR is produced when an incoming stimulus fails to find a match in short-term memory (STM). The mismatch results in a search in long-term memory (LTM), and this cognitive effort results in registration of the novel stimulus in LTM. The processing facilitates later retrieval of the stimulus, but results in inhibition of the OR, because a match is made between the stimulus and memory trace. According to this theory, the OR represents a call for further processing from automatic, pre-attentive mechanisms to a controlled, limited-capacity channel. In this sense, the OR may provide "a gateway to consciousness".

Näätänen (1986) emphasized that, despite sharing certain similarities, the neuronal mismatch mechanism that accounts for the OR is distinct from that underlying the N2 component. Mismatch is a necessary but insufficient condition for the OR. For instance, the degree of change or the magnitude of deviance must be sufficiently large to cause an involuntary shift in attention. When the changes are below detection threshold, the N2a component may still be elicited but the OR will not (Näätänen, 1990).

The Mismatch Negativity Component

In 1975, Näätänen proposed that stimulus change, irrespective of its relevance or of the direction of attention, will produce a specific brain response. The proposed response was later revealed in dichotic listening experiments conducted by Näätänen et al. (1978). In that study,

subjects were instructed to detect occasional deviant stimuli in a sequence presented to a designated ear while ignoring the concurrent sequence of stimuli presented to the opposite ear. The ignored sequence included deviants that were physically identical to the to-be-detected deviants presented in the attended sequence. Deviant stimuli in both the attended and the unattended channels elicited a negativity during the 100 to 200 ms latency range relative to the waveform produced by the standard stimulus in each channel. Thus, the negative wave occurred independent of the subjects' level of attention.

The negativity was seen best in the difference waveform generated by subtracting the averaged response to the standard stimulus from that to the deviant stimulus. The difference wave eliminated any common ERP components elicited by the standard and deviant stimuli, thus indicating the additional processing that the deviant stimulus received. Näätänen et al. (1978) proposed that the difference amplitude reflected the operation of an automatic (i.e., independent of attention) cognitive process used to detect change in the stimulus environment: "It may well be that a physiological mismatch process caused by a sensory input deviating from the memory trace ("template") formed by a frequent "background" stimulus is such an automatic basic process that takes place irrespective of the intentions of the experimenter and the subject, perhaps even unmodified by the latter" (p. 324). Näätänen labeled this change detector the mismatch negativity or MMN.

Characteristics of the MMN Component. The MMN is maximum over fronto-central areas of the scalp and often inverts in polarity at the mastoid when the nose is used as the reference (Alho, Paavilainen, Reinikainen, Sams, & Näätänen, 1986). In humans, the MMN sources have been localized bilaterally in the supratemporal planes of the auditory cortex (e.g., Alho, 1995; Levänen, Ahonen, Hari, McEvoy, & Sams, 1996; Scherg et al., 1989). There may

also be an involvement of parietal regions and of the right frontal-lobe, which is activated by the primary MMN generator and reflects an attentional switching (Giard, Perrin, Pernier, & Bouchet, 1990; Levänen et al., 1996; Opitz, Mecklinger, Von Cramon, & Kruggel, 1999).

The MMN can be elicited by a variety of auditory stimulus changes, including tonal frequency (Näätänen et al., 1978; Sams et al., 1985), intensity (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987a; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993), duration (Näätänen, Paavilainen, & Reinikainen, 1989; Novak, Ritter, & Vaughan, 1992a, 1992b), interstimulus interval (Böttcher-Gandor & Ullsperger, 1992; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987b), and complex stimulus features such as phonemes (Sams, Aulanko, Aaltonen, & Näätänen, 1990) and noise bursts (Sabri & Campbell, 2000). A noise burst is a rather unique complex stimulus in that, by definition, the burst is made up of series of random frequencies and intensities. Nevertheless, noise does elicit an MMN response (Sabri & Campbell, 2000), as reported in Appendix A of this thesis.

Determinants of the MMN Component

Magnitude of Stimulus Change. The MMN is thought to reflect a neural mismatch between the incoming deviant stimulus and the sensory memory formed to the standard stimulus (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989; Ritter, Deacon, Gomes, Javitt, & Vaughan, 1995). As the magnitude of physical deviation increases, the MMN increases in amplitude and its peak latency decreases (Novak, Ritter, Vaughan, & Wiznitzer, 1990; Sams et al., 1985). According to the sensory memory hypothesis, 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 with the memory trace established for the standard stimulus. If a mismatch is detected, the MMN is elicited.

Stimulus-Onset-Asynchrony (SOA). The amplitude of the MMN varies inversely with the rate of stimulus presentation. When slow rates of stimulus presentation are employed, the amplitude of the MMN decreases, probably because the memory trace created for the standard stimulus fades rapidly, before the presentation of the deviant. Repetitions of the standard stimulus create a stronger memory trace and guard it from fading (Ritter et al., 1995). When fast rates are employed, the neuronal trace established for a repetitively-presented standard tone is still active in sensory memory when the deviant arrives. The duration of the neuronal trace has been estimated to be between 2 and 4 s (Mäntysalo & Näätänen, 1987; Näätänen et al., 1987b) (cf. Böttcher-Gandor & Ullsperger, 1992) using electrical recordings, about 10 s using magnetic recordings (Sams, Hari, Rif, & Knuutila, 1993), and up to 20 s according to behavioral studies (Cowan, 1984). The variation in these estimates may stem from the different methodologies used in different studies (e.g., measurement techniques, stimulus parameters, task demands, SOA pattern) (Ritter et al., 1995).

Sequential and Temporal Probability. The amplitude of MMN is inversely related to the probability of occurrence of the deviant: As the probability of deviant occurrence increases, the amplitude of the MMN decreases (Näätänen, 1992; Näätänen, Sams, Järvilehto, & Soininen, 1983). It is not clear, however, whether the determining factor is sequential probability (i.e., the probability of a deviant within a certain number of standards in a block of trials) or temporal probability (i.e., the probability of a deviant within a period of time in a block of trials). A majority of studies report only the sequential probability of deviant occurrence, neglecting its temporal probability. This is unfortunate because, when stimulus-onset-asynchrony (SOA) is

held constant. manipulation of sequential probability will also alter temporal probability. For example. if the SOA is 600 ms and the sequential probability of deviant occurrence is 1(deviant)/15(standards). then the temporal probability of deviant occurrence is. on average. 1(deviant)/9.00 s. If sequential probability of deviant occurrence is changed to 1(deviant)/7.5(standards). then its temporal probability shifts to 1(deviant)/4.50 s.

When sequential probability is held constant. manipulation of SOA alters temporal probability. Increasing the SOA (i.e.. decreasing the rate of stimulus presentation) will decrease the temporal probability. For example. if sequential probability is held constant at 1(deviant)/7.5(standards). increasing the SOA from 150 to 600 ms will decrease the temporal probability from 1(deviant)/1.125 to 1(deviant)/4.50 s. respectively. Conversely. when temporal probability is held constant. manipulation of SOA will alter sequential probability. Increasing the SOA (i.e.. decreasing the rate of stimulus presentation) will increase sequential probability. If temporal probability is held constant at 1(deviant)/9.00 s. for example. increasing the SOA from 150 to 600 ms will increase the sequential probability from 1(deviant)/60(standards) to 1(deviant)/15(standards). respectively. Generally. then. the factors of SOA. temporal probability. and sequential probability are easily confounded. making it difficult to ascertain their independent effects on change detection. The goal of the second experiment in this thesis is to disentangle the effects of these factors on the MMN.

Theories of the MMN Mechanism

The MMN is considered by many to be the neuronal expression of change in auditory sensory memory. Infrequent stimuli alone. without intervening standard stimuli. do not elicit an MMN (Korzyukov. Alho. Kujala. Gumenyuk. Ilmoniemi. Virtanen. Kropotov. & Näätänen.

1999; Näätänen et al., 1989). On this view, the MMN will be elicited only if an echoic memory of the standard stimulus persists at the time the deviant is presented. If the rate of stimulus presentation exceeds several seconds, the estimated duration of echoic memory, the sensory trace of the standard stimuli will gradually decay (Mäntysalo & Näätänen, 1987). Evidence supporting the involvement of memory traces in MMN generation comes mainly from studies in which a masking stimulus either follows (backward masking) or precedes (forward masking) both standard and deviant (Näätänen, 1992). In these studies, short SOAs (<150 ms) produce strong masking effects and a diminished MMN.

An alternative view conceptualizes the MMN as an index of the ease with which a new stimulus is incorporated into the current sensory/perceptual context. On this account, a slow rate of presentation places the deviant far outside the current context, which is why under these conditions the MMN is reduced in magnitude (Cowan, Winkler, Teder, & Näätänen, 1993). Here, the standard acts as a norm and, the longer the SOA, the more distinct the deviant is from the train of standards, which effectively removes it from context. A somewhat similar explanation postulates that the deviance detection system uses the temporal pattern in which stimuli appear as a predictor of the subsequent stimulus (Deacon, Gomes, Nousak, Ritter, & Javitt, 2000; Winkler, Karmos, & Näätänen, 1996). The system is then set for a specific stimulus, but slow rates of presentation weaken its prediction potential.

The Role of Attention on the MMN Component

Remarkably, the MMN is still considered by most researchers to be *largely* independent of factors such as the subject's level of attention or even his or her conscious awareness that a deviant was, in fact, presented. This consensus arises from much of the current evidence, which

suggests that the MMN component is preattentive and automatic. In these studies subjects are tested under two conditions. In one condition, the subjects are asked to attend actively and to detect occurrences of a deviant within a stream of standard stimuli. In the other condition, the subjects are asked to engage in a separate task (e.g., reading a book), and to ignore all auditory stimuli (standards and deviants) that are presented to their ear. Most studies using this paradigm have found that the magnitude of the MMN does not vary in spite of the attentional manipulation.

Evidence of Strong Automaticity of MMN. Näätänen and Gaillard (1983) reported data demonstrating an MMN response in the absence of subjective pitch discrimination. They found that the MMN component was elicited to undetected deviant stimuli in an active discrimination task. This MMN was of approximately the same magnitude as the MMN elicited by correct detections and "not sure" responses. They concluded that the MMN is independent of conscious awareness of the deviant. Sams et al. (1985) systematically explored the effects of different magnitudes of frequency deviation on the MMN in attend and ignore conditions. They found no difference in the magnitudes of MMNs elicited to attended and ignored deviants. Kathmann, Frodl-Bauch, and Hegerl (1999) and Otten, Alain, and Picton (2000), using a continuous visual task, also found that the MMN did not vary with manipulations of attention. Nonetheless, task demands did affect the extent to which the ignored tones were processed: The difficult task resulted in additional processing seen in later ERP components.

One problem with paradigms used to test the role of attention on MMN is that subjects are asked to press a button upon detection of the deviant stimulus in the attended channel. Electrophysiologically, the preparatory motor activation will elicit a negative wave (a negative readiness potential) that overlaps and summates with the MMN (Alain & Woods, 1997).

Moreover, directing attention to the deviant stimulus also will result in the elicitation of the N2b, yet another overlapping negativity. One means of overcoming the interpretive problems of overlapping negativities such as N2b or movement-related ERPs is to include two deviant stimuli in the attend channel, only one of which requires a motor response (Alho, 1992). Under such conditions, the amplitude of the MMNs to the attended and unattended frequency deviants does not differ (Alho, Woods, & Algazi, 1994; Näätänen et al., 1993). In contrast, under these conditions the MMN to intensity deviants has been found to be more susceptible to attentional manipulations (Näätänen et al., 1993; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998).

Evidence for Partial Automaticity of MMN. A challenge to the view that the MMN is unaffected by attention is found in dichotic listening studies in which high rates of stimulus presentation are used to force a strong attentional focus. Under these conditions, unattended stimuli that deviate from standards on the basis of intensity (Woldorff, Hackley, & Hillyard, 1991) or frequency (Alain & Woods, 1997; Trejo, Ryan-Jones, & Kramer, 1995) produce a smaller MMN than attended stimuli. These results suggest that the processes of change detection gauged by the MMN response are only partially automatic.

A similar conclusion has been reached in studies of intermodal selective attention in which subjects are engaged in a primary visual task and are asked to attend to or ignore concurrent auditory stimuli. To-be-ignored auditory frequency deviants elicited MMNs that were attenuated relative to attended auditory deviants (Alho, Woods, Algazi, & Näätänen, 1992; Woods, Alho, & Algazi, 1992). This effect, however, was noted only for small frequency changes and not for large deviants.

Problems in Studying Attentional Effects on MMN. There are, however, several problems in interpreting the results found in these studies. Most important among these is the validity of

the manipulation itself: In the non-attention condition it is very difficult to determine the extent to which subjects are actually ignoring the auditory stimuli. Indeed, it is possible that the subjects may switch their attention between the primary task and the auditory stimuli, even if they are not conscious of this attentional switching.

A second problem is created by the technique of comparing waveforms between the attend and ignore conditions. In the attend condition, the requirement of active detection of a target elicits additional ERPs. In particular, a negative wave, N2b, peaking at about 250 ms and a positive wave, P3, peaking at about 300 ms are elicited by the requirement to detect deviants (see the section *Components Evoked by Stimulus Change*). These components are not elicited in the non-attend condition. The negative attention-elicited N2b component will tend to summate and overlap with the MMN component. Thus, the absence of MMN differences between attend and ignore conditions cannot necessarily be interpreted as the absence of an effect of attention. Whereas negativity in the ignore condition may reflect a true MMN, negativity in the attend condition may reflect the combination of several overlapping positive and negative components. For example, if the MMN overlaps with N2b, a large amplitude negative wave will be observed 200 to 250 ms after stimulus onset. This could be the MMN, the N2b, or a combination of the two.

Using Sleep to Study the Automaticity of MMN

A methodological difficulty in studying automaticity of the MMN component is ensuring that awake and alert subjects actually ignore the deviant stimuli. Subjects will occasionally report their awareness of stimulus change despite their engagement in a primary task (Sams et al., 1985). It is challenging to design an experiment that controls for and quantifies the amount

of attention paid to a putatively ignored channel. Recently, investigators from several laboratories have attempted to overcome this problem by recording the MMN during states of unconsciousness. The unconscious state that is most often studied is natural sleep. Sleep is the period of time during which subjects are probably least attentive to and thus least conscious of the external environment. In order for sleep to occur, it would appear that the processing of all but the most relevant of external stimuli must be inhibited.

Difficulty in Obtaining Behavioral Measures During Sleep. ERPs provide a means to monitor the extent of stimulus information processing during sleep. However, it is difficult to obtain overt detections within sleep (see Campbell, Bell, & Bastien, 1992, for a review). There are several concerns associated with studying mechanisms of change detection during sleep. First, the experimenter does not have access to the subject's mental state because overt behavioral responses to target stimuli can rarely be made. During sleep, muscle tonus may be inhibited; hence subjects might be unable to initiate a motor movement. Moreover, even if subjects are conscious of a stimulus change (sensitivity), they may be unwilling or unable to signal their detection (decision bias). Some researchers awaken the sleeper in order to probe his or her mental state at the time of stimulus presentation. However, any inability to recall the features of the external stimulus may be due to a failure of storage or retrieval of short-term memory rather than to unawareness that the stimulus had been presented. Nonetheless, in the absence of an overt behavioral response, ERPs offer a powerful means to assess the detection of stimulus change during states of unconsciousness. In this regard, the ERP component of choice is the MMN.

Studies of MMN During Unconscious States. A number of previous studies have attempted to elicit the MMN during states of unconsciousness. The MMN to a frequency change

can be elicited in sleeping human newborns (Alho, Sainio, Sajaniemi, Reinikainen, & Näätänen, 1990), and in cats during slow-wave sleep (Csepe, Karmos, & Molnar, 1987). Kane, Curry, Butler, and Cummins (1993) and Fischer, Morlet, Bouchet, Luaute, Jourdan, and Salord (1999) were able to record a frequency-elicited MMN in comatose patients who subsequently emerged from their unconscious state within 2 to 3 days. The MMN also is evident following inhalation of the anesthetic gas nitrous oxide (N_2O), albeit decreased in amplitude (Pang & Fowler, 1999). It is important to note, however, that, in Pang and Fowler's study, the dosage of N_2O did not cause the subject to lose consciousness. They found that the actual number of conscious detections of the deviant was not altered by the anesthetic, although reaction time was prolonged.

The Effects of Sleep on Late ERP Components. The late AEP components, peaking between 50 and 500 ms, are markedly affected by sleep onset (i.e., the transition period from a fully awake conscious state to one of unconsciousness and sleep) and by sleep itself. The onset of sleep results in a gradual decrement in the amplitude of the auditory N1, while P1 and P2 amplitudes can be enhanced (Colrain, Di Parsia, & Gora; 2000; de Lugt, Loewy, & Campbell, 1996; Harsh, Voss, Hull, Schrepfer, & Badia, 1994; Hori, Hayashi, & Morikawa, 1994; Ogilvie, Simons, Kuderian, MacDonald, & Rustenburg, 1991). The collective effect of sleep on these three components is characterized best as an overall loss of a long-lasting negativity, which is thought to be due to inhibition of sensory processing (Campbell et al., 1992). The decrease in the amplitude of N1 is paralleled by a decline in behavioral performance (Noldy, McGarry, & Campbell, 1988; Ogilvie et al., 1991). A reduction in the amplitude of N1-like waves combined with an increase in the amplitude of P2 also has been observed at sleep onset in other modalities. Occlusion of respiration will elicit a similar N1-P2 effect at sleep onset (Gora, Colrain, & Trinder, 1999).

Näätänen (1990) has suggested that N1 may act as a transient-detector system that triggers an internal attentional system. N1 might subserve "conscious perception of auditory stimuli in general...without indicating what the stimulus is or what its precise features are" (Näätänen, 1990, p. 212). During NREM sleep, N1 is near baseline level. The ERP evidence thus suggests that, during NREM sleep, information processing of auditory stimuli is predominately inhibited. Indeed, even general consciousness and awareness of imprecise features of the external stimulus do not appear to be possible in NREM sleep. During REM sleep, N1 and P2 may return to 25-50% of their waking amplitude. Campbell et al. (1992, 2000) claimed that some form of "fuzzy consciousness" may be possible during REM sleep. This, however, would be directly opposed to the view of Hobson and colleagues (Hobson, Pace-Schott, Stickgold, & Kahn, 1998) that awareness of external events is not possible, particularly during REM sleep when mental resources are directed toward internal dream activity.

Studies of MMN During Sleep. There have been several previous attempts to record the MMN component during various stages of sleep. The frequency MMN to deviant tones that are widely discrepant from the standards has been reported in REM sleep, although reduced in amplitude (Atienza & Cantero, 2001; Atienza, Cantero, & Gomez, 1997, 2000; Loewy, Campbell, & Bastien, 1996). When an intensity deviant is employed, however, the MMN cannot be elicited in REM sleep (Loewy, Campbell, de Lugt, Elton, & Kok, 2000). Recently, Atienza and Cantero (2001) have described the MMN to complex auditory patterns. Each stimulus consisted of eight segments of different frequencies. The only difference between the standard and deviant stimuli was an increase of 15% frequency contrast in the sixth segment. Initially, subjects could not distinguish between the standard and the deviant. Because a perceptual discrimination could not be made, the MMN to the deviant was not elicited. Upon training,

subjects learned successfully to discriminate the subtle deviant from the standard. Consequently, the MMN was elicited in both wakefulness and REM sleep.

Most laboratories have been unable to record the MMN in NREM sleep to either frequency deviants (Campbell et al., 1992; Loewy et al., 1996; Paavilainen, Cammann, Alho, Reinikainen, Sams, & Näätänen, 1987; Winter, Kok, Kenemans, & Elton, 1995) or intensity deviants (Loewy, Campbell, de Lugt, Elton, & Kok, 2000). Sallinen, Kaartinen, and Lyytinen (1994) reported the elicitation of a frequency MMN in Stage 2 sleep, but only when the deviant stimulus also elicited a K-Complex. The K-Complex is an extremely large evoked potential that occurs predominantly in NREM sleep (see Bastien, Ladouceur, and Campbell, 2000, for a discussion of the K-Complex). The fact that the MMN is elusive during deeper stages of unconsciousness invites the interpretation that change detection might be a controlled, rather than automatic, cognitive process.

Sallinen and Lyytinen's Study. Perhaps the most thorough previous investigation of the MMN response during sleepiness was conducted by Sallinen and Lyytinen (1997). These researchers studied the MMN to frequency deviants during subjectively (Stanford Sleepiness Scale: alert, intermediate, sleepy) and objectively (physiological criteria: wakefulness, drowsiness, stage 1) rated sleepiness. The subjects' task was to detect either rare auditory targets presented to the right ear or rare changes in light flashes, while ignoring auditory tones presented to the left ear. The unattended tones consisted of a 1000 Hz standard ($p = .90$), a 1050 Hz small deviant ($p = .05$), and a 1200 Hz large deviant ($p = .05$). The amplitude of the MMN decreased significantly as subjectively-rated alertness decreased. In the subjectively-rated alert state and in the objectively drowsy state (defined as an epoch containing at least one slow eye movement), Sallinen and Lyytinen found that an MMN was elicited for the large deviant, but not for the

small deviant. In the subjectively-rated sleepy state, however, no MMN was observed to either deviant. The authors concluded that the withdrawal of attention during states of unconsciousness significantly disrupts change detection as measured by the MMN.

Several considerations jeopardize the conclusions of Sallinen and Lyytinen (1997). Sleep researchers generally agree that Stage 1 (defined according to the traditional criteria put forth by Rechtschaffen & Kales, 1968) marks the transition from waking to sleeping states. Its duration is typically very brief, often lasting only a few minutes. Unfortunately, the limited number of trials included in Sallinen and Lyytinen's (1997) study (a total of 213 trials in the objective sleepy category and a total of 183 trials in the subjectively sleepy category, across all subjects) did not permit reliable ERPs to be recorded in Stage 1 sleep. Moreover, the attentional and response demands in this experiment elicited an N2b-P3 wave which is known to overlap and summate with the MMN. In order for subjects to reject non-target stimuli presented to their unattended channel, they had to first detect them, although this detection could have occurred outside of consciousness. In summary, the research by Sallinen and Lyytinen leaves open serious questions about the role of sleep in the elicitation of the MMN.

Specific Aims of the Thesis

The effects of consciousness/attention on the MMN component remain a subject of controversy. One of the major problems in studying the MMN in awake subjects is in determining the extent to which they attend to stimuli to be ignored (i.e., to what extent are they unable to ignore the stimuli). From a methodological point of view, it is exceedingly difficult to test this question. Obviously, having subjects respond to information in the ignored channel effectively will direct their attention toward it. For this reason, some researchers study the MMN

during unconscious states, such as sleep or under anesthesia. Sleep is the time when subjects are least conscious of the external environment. Within sleep, the MMN has been found to be elicited during REM, although it is reduced in amplitude. The MMN does not appear to occur in NREM sleep. Subjects enter NREM before REM sleep. Thus, during the transition from a fully awake and conscious state to one of NREM sleep and unconsciousness, the MMN may gradually dissipate.

Unfortunately, the critical sleep onset period has not been widely studied. There are also formidable difficulties in doing so. Stage 1 of "sleep" marks the transition from the waking to sleeping state and its duration can be very brief. The amplitude of the MMN is relatively small (often less than 1 μV) while the amplitude of the background EEG during sleep onset can be relatively large (more than 100 μV). The signal (the MMN) to noise (the background EEG) ratio is therefore poor. To reduce the amplitude of the random background EEG, hundreds if not thousands of trials need to be presented. In the usual sleep onset protocol, the duration of Stage 1 is insufficient to permit the presentation of such a large number of trials. Ogilvie et al. (1991) developed a method in which sleepers are awakened repeatedly. This method was employed in the current thesis. A sufficiently large number of trials can be presented as subjects repeatedly pass through Stage 1 sleep.

This dissertation consists of three experiments written in article format appropriate for the journal to which each has been submitted for publication.

Experiment 1: The purpose of this initial study was to evaluate the sensitivity of the frequency MMN to changes in the state of consciousness during the transition from wakefulness to sleep. An often-used MMN paradigm was used in Experiment 1. It is generally accepted that the MMN occurs independent of conscious awareness and attention to the deviant stimuli. From

this perspective, the MMN should be observed during the sleep-onset period. On the other hand, the MMN has not been elicited reliably during NREM sleep. Because NREM sleep occurs mainly in the first half of the night, it thus was expected that MMN would dissipate gradually during sleep onset.

Experiment 2: Stimulus input to the auditory cortex needs to be inhibited in order to maintain sleep. It has been established that such gating occurs in the thalamus, prior to the MMN cortical generating system. The MMN has not been recorded during NREM sleep. Two different explanations might account for this result. By the first account, the failure to observe the MMN during NREM sleep is due to the absence of sensory input to the cortical generators. According to the second account, there is sufficient input for the MMN sensory memory system to function. However, sensory memory fades rapidly during the waking state (within 2-10 s), and may fade even more rapidly during sleep. Most studies present a stimulus every 500 to 1000 ms. Such a rate of presentation may be too slow to elicit the MMN in the sleeping state. The third experiment in this thesis employed a rapid rate of stimulus presentation. The amplitude of the MMN is, however, affected by how often the deviant is presented. It is unclear whether the determining variable is sequential probability or temporal probability. Experiment 2 was needed determine the stimulus parameters for Experiment 3, systematically manipulating sequential probability and temporal probability.

Experiment 3: In Experiment 1, the frequency MMN following the large deviant was still elicited in Stage 2 of sleep, although reduced in amplitude. However, it was not observed during SWS. The MMN following the small deviant could not be detected in Stages 1, 2 or SWS. The purpose of the Experiment 3 was to evaluate whether an MMN can be observed in NREM sleep when stimuli are presented quickly enough to support rapidly decaying sensory

memory. Such evidence would support the hypothesis that, in previous studies, the memory trace of the standard stimuli decayed before the deviant was presented. Failure to observe the MMN when stimuli are presented very rapidly would be consistent with the hypothesis that, during NREM sleep, cortical encoding of both the standard and deviant is weakened because of prior thalamic inhibition of sensory input.

Chapter 2

Experiment 1: The Mismatch Negativity to Frequency Deviants During the Transition from Wakefulness to Sleep

The following manuscript has been published in *Canadian Journal of Experimental Psychology, 54*, 230-242. The present study examines the changes in the Mismatch Negativity during the transition from a waking, conscious state to one of sleep and unconsciousness. Auditory event-related potentials were recorded from eight participants during the sleep onset period. A 1000 Hz standard stimulus was presented every 600 ms. At random, on 20% of the trials, the standard was changed to either a large 2000 Hz or a small 1100 Hz deviant. During wakefulness the large deviant elicited a larger, long-lasting MMN than the small deviant. Following the large deviant during relaxed wakefulness and stage 2 sleep, the MMN continued to be elicited although it was reduced in amplitude. No significant MMN was recorded for either deviant in stages 1 and slow-wave sleep. The loss of consciousness therefore appears to have a marked effect on the MMN.

Summary

A long lasting negative wave, the Mismatch Negativity (MMN) is thought to be elicited automatically upon detection of a rarely presented stimulus that physically deviates from an ongoing train of standard stimuli. The MMN occurs from 100 to 250 ms after the onset of the deviant stimulus. It cannot however be elicited during non-REM sleep. This article examines the changes in the MMN during the transition from a waking, conscious state to one of sleep and unconsciousness. Auditory event-related potentials were recorded from eight participants during the sleep onset period. During the transition from waking to sleeping states, participants pass through a series of stages: relaxed wakefulness, stage 1, 2, 3 and 4. Stages 3 and 4 are often combined to form slow-wave sleep, the deepest stage of sleep. Participants were repeatedly awakened to assure enough stage 1 had accumulated for purposes of analysis. A 1000 Hz standard stimulus was presented every 600 ms. At random, on 20% of the trials, the standard was changed to either a large 2000 Hz or a small 1100 Hz deviant. The large and small deviants had equal chance of presentation. When participants were awake while reading a book (i.e., ignoring the auditory stimuli), both the large and small deviants elicited a long-lasting MMN. The MMN was attenuated following the small deviant. When participants were asked to fall asleep, but were still classified as being awake (i.e., relaxed wakefulness), the MMN following the large deviant was attenuated while the MMN following the small deviant could not be detected. The small deviant MMN could also not be detected in stage 1, 2 or slow-wave sleep. The large deviant MMN was also not observed during stages 1 and slow-wave sleep. It was however still elicited, although reduced in amplitude in stage 2 of sleep. The loss of consciousness therefore appears to have a marked effect on the MMN. During sleep, it is

possible that information processing is inhibited prior to input to the cortical module responsible for the generation of the automatically-elicited MMN.

Introduction

The purpose of the present study was to determine the effects of loss of consciousness on the apparently automatic detection of physical deviance. A fundamental role of the nervous system is to detect change in the external environment. Over the past 25 years, Risto Naatanen and his Finnish colleagues have extensively examined the neurophysiology of change/deviant detection in human participants. When a participant is presented with a deviant auditory stimulus occurring infrequently in a sequence of otherwise repetitive, homogeneous standard auditory stimuli, a mismatch negativity (MMN) is elicited (Naatanen, Gaillard, & Mantysalo, 1978). The MMN is a negative event-related potential (ERP) wave that is maximal at fronto-central areas of the scalp and often inverts in polarity at the mastoid (the large bony region behind the ear) when the nose is used as the reference (Alho, Paavilainen, Reinikainen, Sams, & Naatanen, 1986). This is because the dipole sources of the MMN are located in the auditory cortex. It is recorded as a negative deflection at scalp sites superior and as a positive deflection at scalp sites inferior to the auditory cortex. The MMN can begin as early as 50 ms and last up to 300 ms after deviant onset. The MMN can be elicited by a variety of auditory stimulus changes, including tonal frequency (Naatanen et al., 1978; Sams, Paavilainen, Alho, & Naatanen, 1985), intensity (Naatanen, Paavilainen, Alho, Reinikainen, & Sams, 1987; Naatanen, Paavilainen, Tiitinen, Jiang, & Alho, 1993), duration (Naatanen, Paavilainen, & Reinikainen, 1989; Novak, Ritter, & Vaughan, 1992a, 1992b), interstimulus interval (Bottcher-Gandor & Ullsperger, 1992), and complex stimulus features such as phonemes (Sams et al., 1990) or noise (Sabri & Campbell, 2000).

An auditory stimulus will elicit a series of long-latency components that peak from 50 to 300 ms. An early, small amplitude positive wave, P1, peaks at about 50 ms. It is followed by a well-documented negative-positive wave, N1-P2. N1 peaks at about 80 ms and P2 peaks from 180 to 250 ms. A later negative wave, N2, peaking between 200 and 300 ms can often be recorded. The MMN is a small amplitude (typically less than 2 μV) subcomponent of the negative wave, N2. Naatanen, Simpson, and Loveless (1982) demonstrated that N2 is comprised of at least two subcomponents. The first, labeled N2a, represents the automatically (i.e., independent of attention) elicited MMN. The second, labeled the N2b, has a slightly longer latency and appears as a sharper negative peak superimposed on the descending N2a. The N2b wave may be followed by a late positive wave, P3a. The P3a is maximal over fronto-central areas of the scalp and peaks between 250-350 ms. Sams, Paavilainen, Alho, and Naatanen (1985) noted that the N2b-P3a wave may be elicited for widely deviant stimuli that are very different from the standard stimuli in conditions in which participants are instructed to ignore the stimuli. Although engaged in a primary task (e.g., reading), participants can be distracted by and switch attention to a very discrepant deviant. The MMN-N2b process thus provides a means by which participants can become conscious of the deviant stimulus. When participants are asked to actively detect the rare, deviant stimulus, a later parietal positivity, the P3b (or "P300" since it occurs at about 300 ms) is elicited. There is very good evidence that P300 reflects conscious detection and classification of the rare deviant stimulus (Picton, 1992).

The MMN is thought to reflect a neural mismatch between the incoming deviant stimulus and the sensory memory formed to the standard stimuli (Naatanen, Paavilainen, Alho, Reinikainen, & Sams, 1989; Ritter, Deacon, Gomes, Javitt, & Vaughan, 1995). As the magnitude of physical deviation increases, the MMN increases in amplitude and its peak latency

decreases (Sams et al., 1985). According to the sensory memory hypothesis, 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.

MMN and Attention

Remarkably, the MMN is thought to be largely independent of factors such as the participant's level of attention or even his or her conscious awareness that a deviant was, in fact, presented. The MMN appears to operate in the preconscious. Evidence supporting the notion that the MMN is independent of participants' conscious awareness comes from studies that manipulate attention. Participants might be asked to actively attend to and detect the deviant in one condition, and to ignore the stimuli while engaged in a primary task (e.g., reading a book) in another. In most studies, the MMN does not vary in spite of various attentional manipulations. There are, however, problems with the usual attentional paradigm. Most importantly, in the ignore condition it is very difficult to determine the extent to which participants are actually ignoring the stimuli. It is possible that they may switch attention between the primary task and the auditory stimuli, even if they are not conscious of this switching. In the attend condition, the requirement of active detection of a target causes other methodological problems. Detection of the deviant elicits additional evoked potentials. A negative wave, N2b, peaking at about 250 ms and a positive wave, P3, peaking at about 300 ms will be elicited in attend but not ignore conditions. These will summate and overlap with the MMN. Thus variation in the MMN could either be interpreted as a result of attention to the deviant or the fact that other negative and positive components have also been elicited. For example, if the MMN overlaps with N2b, a

large amplitude negative wave will be observed 200 to 250 ms after stimulus onset. This could be the MMN, the N2b, or a combination of the two.

Naatanen and Gaillard (1983) reported data demonstrating the presence of a MMN in the absence of subjective pitch discrimination. In an active discrimination task, the MMN was found to be elicited for undetected deviant stimuli and was of about the same magnitude as that elicited for correct detections and "not sure" responses. Sams et al. (1985) systematically explored the effects of different magnitudes of frequency deviation on the MMN in attend and ignore conditions. These authors did not find differences between the MMN elicited for the attended and ignored deviants. Otten, Alain, and Picton (2000) also found that MMN did not vary with manipulations of attention using a continuous visual task. However, task demands did affect the extent to which the ignored tones were processed. The difficult task resulted in additional processing seen in later ERP components.

A challenge to the view that the MMN is not affected by attention was brought about by results of dichotic listening studies designed to force a strong attentional focus by using high rates of stimulus presentation. Under these manipulations, stimuli that deviated from standards on the basis of intensity (Woldorff, Hackley, & Hillyard, 1991) or frequency (Alain & Woods, 1997; Trejo, Ryan-Jones, & Kramer, 1995) produced a smaller MMN when presented to the unattended ear than when presented to the attended ear. Intermodal selective attention experiments involving auditory and visual tasks also showed that when engaged in a visual task, to-be-ignored auditory frequency deviants elicited MMNs that were attenuated relative to attended auditory deviants (Alho, Woods, Algazi, & Naatanen, 1992; Woods, Alho, & Algazi, 1992). This effect was, however, only noted for small frequency changes and not for large deviants. A problem with selective attention paradigms is that the participant is usually asked to

press a button upon detection of the rare deviant stimulus in the attended channel. The preparatory motor activation will also elicit a negative wave (a negative readiness potential) that overlaps and summates with the MMN (Alain & Woods, 1997). Directing attention to the deviant stimulus will also, as already mentioned, result in the elicitation of yet another overlapping negativity, the N2b. A means to overcome the overlapping negativities such as N2b or movement-related ERPs (Alho, 1992) is to incorporate two deviant stimuli in the attend channel, only one of which requires a motor response (Alho, Woods, & Algazi, 1994; Naatanen et al., 1993). Under such conditions, the amplitude of the MMNs to the attended and unattended frequency deviants did not differ. Nevertheless, the MMN to intensity deviants has been found to be more susceptible to attentional manipulations (Naatanen et al., 1993; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998).

MMN During Sleep

A methodological difficulty with the study of the MMN is determining the extent to which awake and alert participants are actually ignoring the deviant stimuli. Participants will occasionally report awareness of the deviant stimuli despite their engagement in a primary task (Sams et al., 1985). It is not easy to design an experiment that controls for and quantifies the amount of attention paid to an apparently to-be-ignored channel. Some authors have attempted to overcome this by recording the MMN during states of unconsciousness. The unconscious state that is most often studied is natural sleep. Sleep is the period of time in which participants are probably least conscious of the external environment. In order for sleep to occur, it would appear that the processing of all but the most relevant of external stimuli must be inhibited. ERPs provide a means to monitor the extent of inhibition of information processing during sleep (see Campbell, Bell, & Bastien, 1992 for a review). There are, however, many difficulties

associated with studying information processing during sleep. The experimenter does not have access to the participant's mental state. Overt responses to target stimuli are rarely made. Even though participants might be conscious of a stimulus, they may be unwilling or unable to signal their detection. Some researchers awaken the sleeper in order to probe his or her mental state at the time of stimulus presentation. The inability to recall the features of the external stimulus may be due to a failure of storage or retrieval of short-term memory rather than an absence of conscious awareness that the stimulus had been presented. In the absence of an overt behavioral response, ERPs offer a powerful means to monitor the extent of information processing during sleep.

A number of studies have attempted to elicit the MMN during states of unconsciousness. The MMN to a frequency change can be elicited in sleeping human newborns (Alho, Sainio, Sajaniemi, Reinikainen, & Naatanen, 1990), and in cats during slow-wave sleep (Csepe, Karmos, & Molnar, 1987). Kane, Curry, Butler, and Cummins (1993) and Fischer et al. (1999) were able to record a frequency-elicited MMN in comatose patients who within 2 to 3 days emerged from their unconscious state. In addition, the MMN is evident following an inhalation of the anesthetic gas nitrous oxide (N_2O), albeit decreased in amplitude (Pang & Fowler, 1999). In Pang and Fowler's study, the dosage of N_2O did not cause the participant to lose consciousness. The actual number of conscious detections of the deviant was not altered although reaction time was prolonged.

The late components of the auditory ERP, peaking between 50 and 500 ms, are markedly affected by sleep onset (i.e., the transition period from a fully awake conscious state to one of unconsciousness and sleep) and by sleep itself. The onset of sleep results in a gradual decrement in the amplitude of the auditory N1, while P1 and P2 amplitudes are enhanced (Ogilvie, Simons,

Kuderian, MacDonald, & Rustenburg, 1991; Harsh, Voss, Hull, Schrepfer, & Badia, 1994; De Lugt, Loewy, & Campbell, 1996). This overall loss of a long-lasting negativity is thought to be due to inhibition of sensory processing (Campbell et al., 1992). The decrease in amplitude of N1 is paralleled by a decline in behavioral performance (Noldy, McGarry, & Campbell, 1988; Ogilvie et al., 1991). The decline in the amplitude of N1 and increase in the amplitude of P2 has also been observed at sleep onset in other modalities. Occlusion of respiration will elicit a similar N1-P2 effect at sleep onset (Gora, Colrain, & Trinder, 1999). Naatanen (1990) has suggested that N1 may act as a transient-detector system that triggers an internal attentional system. N1 might subserve "conscious perception of auditory stimuli in general...without indicating what the stimulus is or what its precise features are" (Naatanen, 1990, p. 212). During non-REM sleep, N1 is near baseline level. Therefore, current ERP evidence during sleep strongly suggests that information processing is largely inhibited in non-REM sleep. Thus, even general consciousness and awareness of imprecise features of the external stimulus do not appear to be possible in non-REM sleep. During REM sleep, N1 and P2 may return to 25-50% of their waking amplitude.

There has been some attempt to record the MMN during sleep. The frequency MMN to widely deviant tones has been reported in REM sleep, although reduced in amplitude (Atienza, Cantero, & Gomez, 1997; Loewy, Campbell, & Bastien, 1996). However, when an intensity deviant is employed, the MMN cannot be elicited in REM sleep (Loewy, Campbell, De Lugt, Elton, & Kok, 2000). Most laboratories have been unable to record the MMN in non-REM sleep to either frequency (Campbell et al., 1992; Loewy et al., 1996; Paavilainen et al., 1987; Winter, Kok, Kenemans, & Elton, 1995) or intensity deviants (Loewy et al., 2000). Sallinen, Kaartinen, and Lyytinen (1994) reported the elicitation of a frequency MMN in stage 2 sleep, but only when

the deviant stimulus also elicited a K-Complex. The K-Complex is an extremely large evoked potential that occurs predominantly in non-REM sleep (see Bastien, Ladouceur, and campbell, this issue, for a discussion of the K-Complex).

Most of REM sleep occurs late at night while much of the early sleep process is dominated by non-REM sleep (stages 2, 3 and 4), a period of time in which the MMN is difficult to elicit. The transition from a waking to a sleeping state should thus have a marked effect on the MMN. Sallinen and Lyytinen (1997) studied the MMN to frequency deviants during subjectively (Stanford Sleepiness Scale: alert, intermediate, sleepy) and objectively (physiological criteria: wakefulness, drowsiness, stage 1) rated sleepiness. The participants' task was to detect either rare auditory targets presented to the right ear or rare changes in the light flashes, while ignoring auditory tones presented to the left ear. The unattended tones consisted of a 1000 Hz standard (p = .90), a 1050 Hz small deviant (p = .05), and a 1200 Hz large deviant (p = .05). The amplitude of the MMN decreased significantly as subjectively-rated alertness decreased. In the subjectively-rated alert state, an MMN was elicited for the large deviant but was not reliable for the small deviant. During the intermediate state, the MMN was reliable for both small and large deviants. In the subjectively-rated sleepy state, no MMN was observed. The MMN was elicited only for the large deviant in the objectively drowsy state (defined as an epoch containing at least one slow eye movement). Sleep researchers generally agree that stage 1 (as defined according to the traditional criteria put forth by Rechtschaffen & Kales, 1968) marks the transition from waking to sleeping states. Its duration is typically very brief, often lasting only a few minutes. Unfortunately, the number of trials (a total of 213 trials in the objective sleepy category and a total of 183 trials in the subjectively sleepy category, across all participants) in Sallinen and Lyytinen's study did not permit reliable ERPs to be recorded in

stage 1 sleep. Moreover, the attentional and response demands in this experiment elicited an N2b-P3 wave which is known to overlap and summate with the MMN. In order for participants to reject non-target stimuli presented to their unattended channel, they had to first detect them, although this detection could have occurred outside of consciousness.

Hypotheses

The present study recorded the MMN during the transition from wakefulness to sleep. Optimal conditions were employed for MMN elicitation, such as rapid rate of presentation, low attentional demands, and large degree of deviance between the standard and deviant. A motor response was not required in order to avoid elicitation of other negativities that may overlap with the MMN. ERPs were recorded during definitive wakefulness, during the transition from wakefulness to sleep, and during definitive sleep.

It was expected that the MMN would be attenuated when the extent of deviance between the standard and deviant was reduced. If the MMN is indeed unaffected by participants' conscious state, it would be expected to be elicited during the transition from a waking to a sleeping state and during definitive sleep. On the other hand, if the MMN is dependent on participants' level of consciousness, it might be expected that the MMN would become gradually reduced in amplitude during the transitional period and markedly attenuated during definitive sleep.

Method

Participants

Eight (1 man, and 7 women) healthy, right-handed undergraduate university students volunteered to participate in this study. Participants were between the ages of 21 and 32 (mean = 24.7 years, SD = 3.7 years). All were self-reported good sleepers with no history of hearing or neurological disorders. Participants were instructed to refrain from alcohol and caffeine use within 24 hours of testing. Prior to testing, each participant signed a consent form. All participants received an honorarium for their participation in this study.

ERP recordings

The electroencephalogram (EEG) and electrooculogram (EOG) were recorded using Grass gold-cup electrodes. They were filled with electrolytic gel, and affixed to the skin by surgical tape and to the scalp by collodion-soaked gauze. The EEG was recorded from six scalp locations placed at midline frontal, central, parietal, and occipital sites, the right mastoid, and the mid-point between the right mastoid and the frontal site. The reference was the nose. The electrooculogram was recorded from an electrode placed 1 cm above the outer canthus of the left eye and another placed 1 cm below the outer canthus of the right eye. Both horizontal and vertical eye movements could therefore be recorded using a single polygraphic channel. Blinks and saccadic eye movements (associated with reading, while the participant was awake) could easily be distinguished from the horizontal slow eye movements that appeared in stage 1 sleep. A ground electrode was placed on the forehead. Inter-electrode impedances were kept below 5 kΩ. Stimulus presentation and data collection were controlled by InstEP Systems™ hardware and software. ERP data were collected using two linked microcomputers. The physiological

signals were amplified on a Nihon Kohden model 4314B polygraph. Analog low and high filter settings were 0.3 and 35 Hz, respectively.

The EEG and electrooculogram data were digitized at a 256 Hz sampling rate, using a 12-bit analogue-to-digital (A/D) converter and stored continuously to hard disk. Off-line, the continuous data were reconstructed into discrete trials or "sweeps". A sweep began 50 ms prior to stimulus onset and continued for another 500 ms following it (i.e., the total sweep time was 550 ms). A 20-Hz digital high filter was later applied to the ERP data. The digital filter operated in the frequency domain employing an inverse Fourier (FFT) algorithm.

Stimuli

Evoked potentials were elicited using standard 1000 Hz tone pips (60 dB HL; 50 ms duration; rise/fall time of 5 ms). Two different infrequently occurring deviant stimuli were employed. The pitch of the large deviant was 2000 Hz while that of the small deviant was 1100 Hz. The auditory stimuli were synthesized using an InstEP Systems' 16-bit waveform generator card. Stimulus probability was 0.80 for the standard stimuli and 0.10 for each of the two deviant stimuli. Stimuli were presented at a constant stimulus onset asynchrony (SOA, onset-to-onset) of 600 ms. A total of 1000 trials was presented per block. Standard and deviant stimuli occurred pseudo randomly with the restriction that two deviants could not be presented consecutively. All auditory stimuli were presented monaurally to the left ear via a specially designed, individually fitted hearing aid device. The hearing aid system assured constancy of auditory input in the participant in spite of possible changes in head or body position (Campbell and Bartoli, 1986). A Bruel and Kjaer 2209 sound level meter equipped with a 2 cm^3 coupler was used to calibrate the auditory signals.

Procedure

Participants were instructed to arrive at the laboratory approximately two hours before their normal bedtime. At that time, electrodes were affixed and baseline testing took place. Testing began during the waking state when participants were asked to lie on their backs and to read a book (alert wakefulness condition). The electrooculogram was monitored to ensure that participants continued reading. Upon completion of the alert wakefulness condition, the lights were turned off and the participants were allowed to fall asleep. Testing continued throughout the sleep onset period and included relaxed wakefulness, and stages 1 and 2 of sleep. Some participants also entered stages 3 and 4 of sleep within a block of trials. In order to maximize the amount of data collected during the relatively short sleep onset period, each participant was awakened repeatedly, approximately once every hour. At least five onset periods were obtained for each participant. In five cases, time permitted the collection of an additional sleep onset condition. To verify that the participant was awake, he or she was asked a simple question. Once the participant was awakened and had correctly answered the simple question, he or she was then allowed to resume sleep at which point stimulus presentation began again. The ERP data were stored for further analyses only if the transition from wakefulness to sleep was captured within a block of trials. A minimum of 5000 trials was presented during the sleep onset period per participant (i.e., 4000 standards, 500 large and 500 small deviants).

Data scoring and analysis

Single trial data were rejected off-line if either the EEG or electrooculogram amplitude exceeded $\pm 100 \mu V$ during wakefulness or stage 1 sleep. Unusually large amplitude eye movements (typically saccades while reading) or eye blinks occurring within the 550 ms sweep time would thus be rejected during the waking state. Similarly, large-amplitude, slow horizontal

eye movements occurring within the sweep in stage 1 sleep would also result in rejection of trials. However, this was a relatively rare occurrence (less than 2%). While slow horizontal eye movements commonly occur during stage 1 sleep, the rejection criteria required that they occur during the 550 ms sweep time and that their amplitude exceeds ±100 μV. Single trial data in stage 2, 3 or 4 sleep were rejected if either the electrooculogram or EEG amplitude exceeded ±150μV (to permit inclusion of high amplitude delta waves).

The different stages of wakefulness and sleep were classified by two experienced polysomnographic technologists according to the criteria of Rechtschaffen and Kales (1968). In cases of stage ambiguity, the epoch was excluded from further analysis. Single trial ERPs were sorted into five different sleep/wake stages: alert wakefulness (the reading condition), relaxed wakefulness (lights out with eyes closed), stage 1 sleep, stage 2 sleep, and slow-wave sleep (combined stages 3 and 4 sleep). Relaxed wakefulness was defined by a predominance (> 50%) of low voltage alpha EEG activity (8-12 Hz), and occasional rapid eye movements or blinking. Stage 1 sleep was defined by a loss of alpha (< 50%), a predominance of relatively low voltage theta EEG activity (4-7 Hz), and the presence of slow rolling eye movements. The duration of stage 1 varies widely among sleepers. It can last less than one minute or up to several minutes. Following stage 1 sleep, the sleeper will typically enter stage 2. This stage was defined by the presence of sleep spindles (bursts of 12-14 Hz, rhythmic EEG activity) and K-Complexes in a background of relatively low voltage theta EEG activity. Stage 2 sleep occurs throughout the night. The initial duration of stage 2 following sleep onset lasts from a few to several minutes. Following stage 2 sleep, the sleeper typically enters stage 3 and 4 of sleep. Stage 3 was defined by moderate amounts (25 to 50%) of high amplitude slow delta wave activity (0.5-4 Hz). Stage 4 was defined by large amounts (> 50%) of high amplitude slow delta wave activity

(Rechtschaffen & Kales, 1968). Stages 3 and 4 are often combined and labeled as slow-wave sleep. Most of slow-wave sleep accumulates in the first half of the night. The initial duration of slow-wave sleep can last from 30 to 60 minutes.

Single trial ERPs were corrected for baseline variation and subsequently sorted and averaged within each sleep/wake stage. Separated averages were computed for the standard and deviant stimuli. The data were then collapsed across all sleep onset periods. The MMN is best observed in a subtraction waveform. This is based on the assumption that if the processing of standard and deviant stimuli is identical, the ERPs to both would be identical. The subtraction waveform thus removes processing that is common following both stimuli. What remains is the difference in processing. The difference waveforms were computed by subtracting, point-by-point, the standard from the deviant waveforms at each electrode site within each sleep/wake stage. The 500 ms post stimulus 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. The average of all data points in the 50 ms pre-stimulus period served as a zero amplitude baseline from which all amplitudes were measured. Confidence intervals were then computed for each of the 10 latency intervals in order to evaluate whether the mean amplitudes of all subjects for each interval significantly differed from zero baseline. This procedure is equivalent to computing a *t*-test between the standard and deviant waveforms (Winer, 1971). To restrict the likelihood of a chance finding, the time window of occurrence and the scalp topography were constrained to conform to that observed in literature. The MMN had to occur only within a 100-350 ms time window after stimulus onset and be larger frontally/centrally than parietally. In addition, a polarity inversion had to be observed at the mastoid (M2).

Results

The sleep onset latencies, defined as the delay from the start of stimulus presentation to the start of stage 1 sleep, ranged from 184 s during the first sleep onset period to 87 s during the fifth sleep onset period. There was, however, no general trend among the five replications toward a shorter sleep onset time. Overall, the mean sleep onset latency was 111 s. It should be noted that the relatively fast sleep onset latencies were confounded by the experimental paradigm. The data were analyzed further only when a full transition from wakefulness to stage 2 sleep occurred. If the participant did not fall asleep during the presentation of the 1000 stimuli (i.e., the sleep onset period exceeded 10 min), the data were rejected from further analysis. The mean number of averaged standard trials per participant within the alert wakefulness, relaxed wakefulness, stage 1, stage 2, and slow-wave sleep stages were 1070, 1142, 653, 2611 and 1072, respectively.

Large deviance

The grand-averaged waveforms to the standard and large deviant stimuli in the different waking and sleeping conditions are superimposed in Figure 1. In the alert wakefulness condition (while the participant read a book), a distinctive N1-P2 wave was observed. The N1 and P2 following both standards and deviants peaked at 90 and 205 ms, respectively. The grand-averaged difference waveforms for large deviants in the different waking and sleeping conditions are superimposed in Figure 2. When participants were awake and alert, a long-lasting negative difference waveform was visible. This frontal MMN was significant in both the 100-150 and 150-200 ms intervals. The mastoid (M2) showed a polarity inversion in both intervals.

----------Insert Figure 1 and 2 about here---------

The amplitudes of N1 and P2 following the standard stimulus were markedly affected during the sleep onset period. A two-way ANOVA with repeated measures on electrode site and stage of sleep was employed to compare the changes in N1 and P2 amplitudes. A significant main effect of Stage was noted for N1. $F(4,24) = 10.00$, $MSE = 6.83$, $p < .05$. It was significantly attenuated during stage 1 compared to relaxed wakefulness. A significant Site x Stage interaction was observed for P2 amplitude. $F(12,72) = 4.72$, $MSE = 12.13$, $p < .05$. At midline frontal and central sites, P2 was significantly larger in stage 1 compared to relaxed wakefulness.

During relaxed wakefulness, the frontal MMN in the 100-150 ms window remained statistically significant ($p < .05$) and did not differ significantly in amplitude from that in alert wakefulness ($t < 1$). The MMN observed in the relaxed waking state was not long-lasting. The later 150-200 ms negativity was much attenuated and not significant. A unique large amplitude positive wave (P3a) was observed following the deviant stimulus in the relaxed wakefulness condition. It was maximum over fronto-central sites of the scalp, peaking at 255 ms. This P3a was not visible in the alert wakefulness condition or in any of the sleep conditions.

A small amplitude MMN-like wave was observed during stage 1 but its amplitude was not significantly different from the baseline level. The MMN observed in stage 1 was reduced by approximately 55% relative to the alert wakefulness MMN. A larger and significant 100-150 ms negativity was however observed during stage 2 sleep. $t(7) = 2.37$, $p < .05$. It also inverted in polarity at the mastoid. In stages 1 and 2, a later 150-200 ms negativity could not be observed. No MMN was elicited in slow-wave sleep.

In both stage 1 and 2, a late negative wave peaking on average at 330 ms was apparent. This late negativity was larger at the central site. It was significantly larger following the deviant than the standard, $t(7) = 3.49$, $p < .05$.

Small deviance

The grand-averaged waveforms to the standard and small deviant stimuli in the different waking and sleeping conditions are superimposed in Figure 3. In the alert wakefulness condition, a clear N1-P2 wave, peaking at 90 and 220 ms, respectively, was identified for both standards and deviants. The grand-averaged difference waveforms in the different waking and sleeping conditions are superimposed in Figure 4. When participants were awake and alert, a small but significant MMN was evident in the difference waves in both the 100-150, and 150-200 ms intervals, $t(7) = 2.15$, 2.86, respectively, $p < .05$. The frontal MMN was reduced by approximately 50% compared to that of the large deviant in the same condition. The mastoid (M2) showed a polarity reversal but only in the 100-150 ms interval.

----------Insert Figure 3 and 4 about here---------

Within relaxed wakefulness, no significant negative difference wave could be identified in any time interval. A significant fronto-central P3a, peaking at 258 ms was again elicited. During stage 1, a small but nonsignificant 100-150 ms negativity was observed. This was followed by a larger and significant negativity in the 150-200 ms period. During both stage 2 and slow-wave sleep, there was no evidence of MMN in any time interval.

Discussion

The morphology of the waking auditory ERPs was quite similar to those reported in the literature. The usual N1-P2 wave was observed for the standard stimulus. A long-lasting MMN was apparent following the deviant stimuli. It was significantly larger in amplitude following the large compared to the small deviant. The amplitude of the MMN has been found to be dependent on the extent of deviance in many studies. In the present study, the extent of mismatch in the large deviant condition was unusually large. This will result in the enhancement of the N1 component, that peaks at about 80 to 100 ms, and also in the elicitation of an overlapping MMN at the time of N1. Neurons in the auditory cortex show tonotopic features (Alho, 1995). They respond selectively to specific frequencies. A population of neurons will only respond to a specific frequency and frequencies that are close to this frequency. Widely discrepant frequencies (such as the 1000 and 2000 Hz frequencies used in the large deviant condition) will activate different neuronal populations. The standard stimuli were presented more frequently than were the 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 (Naatanen, 1992). The small deviant would be less likely to activate entirely novel neuronal populations. The 150-200 ms negativity probably reflected a mismatch process that was independent of the N1.

A number of changes emerged during the sleep onset process. Initial differences arose when participants were asked to stop reading their books and to fall asleep. The initial MMN remained apparent; however, its duration was very brief. This may be because both the large and small deviants elicited also a long-latency positivity, the P3a, peaking at about 250 ms (Squires,

Squires, & Hillyard, 1975). A N2b-P3a wave can be elicited in awake and inattentive participants by particularly obtrusive deviant stimuli (Naatanen et al., 1982). When participants were awake and alert, their attention was directed elsewhere, reading a book. This may have prevented the distractions reflected in the P3a process. In the relaxed wakefulness condition, participants were less able to direct their attention away from the obtrusive stimuli. The presence of the P3a provides convincing evidence that participants were unable to inhibit processing of the deviant stimulus when initially attempting to fall asleep. As such, the deviant might thus have intruded into consciousness, thus preventing sleep. A problem with this interpretation is that the P3a is usually preceded by a large negative wave, the N2b. This was not observed in the relaxed wakefulness condition. Another problem with the distraction hypothesis is that it is based strictly on an interpretation of the physiological data. In the present study, there was no independent performance data to support this hypothesis. In some sleep onset studies, the participant's behavioral response to a target stimulus has been employed (Harsh et al., 1994; Noldy et al., 1988; Ogilvie et al., 1991; Sallinen et al., 1997). Overt detection of the target is used as behavioral evidence that the participant is indeed conscious of it. Unfortunately, there are other problems associated with overt responding. It would appear that directing attention to the deviant target stimulus will, in itself, delay sleep. Moreover, the active detection of deviant stimuli will result in additional potentials: a negative movement-related potential, the N2b and a late positive wave, P3b. The negativities will overlap and summate with the MMN, making its interpretation difficult. For this reason, overt responding was not employed in the present study.

The P3a was not observed in either stage 1, stage 2, or slow-wave sleep. When the small deviant was presented, the MMN was similarly not elicited in either stage 1, stage 2, or slow-wave sleep. Thus, when participants began to enter sleep, the MMN no longer could be elicited

by small and unobtrusive deviants. The early portion of the MMN did remain apparent following the large deviant in stage 1, although it was much reduced in amplitude. Somewhat surprisingly, a significantly larger MMN was observed in stage 2 sleep. Most sleep studies have indicated that the MMN cannot be elicited in stage 2 of sleep. Sallinen et al. (1994) have shown, however, that deviant stimuli can elicit an MMN if they also elicit a very large amplitude (>100 μV) negative wave, the K-Complex, that occurs 300 to 600 ms after stimulus onset. In the present study, there was little evidence of K-Complex activity. In the 300-500 ms period, only a small negativity was apparent. The results of the present study therefore appear to contradict the general finding that the MMN cannot be elicited in stage 2 sleep. This study, however, focused on stage 2 activity occurring very shortly after sleep onset. Stage 2 will occupy almost half of the young adult's entire sleep period (i.e., about 4 hours). Previous studies have averaged MMN over this very long period of time. Indeed most studies do not present stimuli during the initial 5-15 minutes of stage 2 sleep, a period of time closely monitored in this study.

The finding of a larger MMN in stage 2 than in stage 1 is not easily explained. Many sleep onset studies have now indicated that participants are at least partially able to make overt detections of external stimuli during stage 1 of sleep. Overt responses are extremely rare during stage 2. As such, it would have been expected that the preconscious MMN would have been larger in stage 1 than in stage 2. Some authors subdivide stage 1 based either on the presence or absence of an overt response, or the frequency spectrum of the EEG. For example, Gora et al. (1999) and Colrain, Di Parsia, and Gora (this issue) have noted marked differences in respiratory and auditory evoked potentials during stage 1 depending on whether the EEG contained mainly higher frequency alpha (8-12 Hz) or lower frequency theta (4-7 Hz) activity. This sub-division of stage could not be carried out in the present study. The duration of stage 1 was very short.

Almost four times as many trials were presented in stage 2 compared to stage 1. Thus, in spite of the fact that participants were awakened repeatedly in order to maximize the number of trials that were presented in stage 1, it is possible that a significant amount of background noise remained in the stage 1 average.

Neither the early nor the later portions of the MMN could be observed in slow-wave sleep for either deviant. This is consistent with other studies. Slow-wave sleep, of course, occurs in the later portion of the sleep onset period, after the occurrence of stages 1 and 2. There is thus little evidence of even preconscious processing in slow-wave sleep. Filter settings can have a marked effect on ERPs. Slow wave sleep is dominated by delta activity. The MMN may last up to 300 ms after deviant onset. The frequency spectrum of the MMN may be similar to that of delta activity. It is therefore possible that the MMN may have been obscured by delta activity. When delta was attenuated by applying a 3 Hz digital high pass filter to the data, few changes were, however, observed in the ERP waveforms.

Naatanen, Paavilainen, Tiitinen, Jiang and Alho (1993) have proposed that two different populations of neurons in the supratemporal region of the temporal lobe are involved in the generation of the MMN. Computational neurons automatically detect the mismatch between the standard and the deviant stimulus. Amplifying neurons determine the magnitude of the response. Naatanen (1991) has suggested that manipulation of attention mainly affects the amplifying neurons. Hence attention that is strongly focused away from the auditory stimuli may result in a suppression of the magnitude of the MMN, even though the preconscious detection of the deviant stimulus has been made. This could explain the attenuated MMN during stage 1 and 2 when a deviant is physically much different from the standard. On the other hand, it would appear that the computational neurons are not able to detect deviants that are much more similar

to the standards in the sleep onset period and during definitive sleep. As sleep progresses and the participant enters slow-wave sleep, the computational neurons do not appear to be able to detect even very large mismatches.

There are other explanations for the failure to observe the MMN. The MMN is thought to reflect echoic sensory memory. A neural representation of the frequently occurring standard stimulus is well-formed and held briefly in sensory memory. The incoming deviant stimulus is then compared to the memory representation for the standard. The MMN will be generated only if the deviant is presented before the memory for the standard fades. In waking states, the duration of this sensory memory has been estimated to be about 4 s using electrical recordings and about 10 s using magnetic recordings of the MMN (Sams, Hari, Rif, & Knuutila, 1993). In the present study, stimuli were presented every 600 ms. Many studies have demonstrated that this relatively rapid rate of stimulus presentation will elicit a large MMN. A large MMN was observed when participants were awake and reading a book. However, it is possible that the rate was too slow to maintain the sensory memory trace at sleep onset and within sleep. The sensory memory might fade very rapidly as participants lose consciousness. A much more rapid rate of stimulus presentation may be required to elicit the MMN in unconscious states.

Alternatively, it is possible that during sleep, incoming sensory information is inhibited prior to entry to the MMN generators in the supratemporal plane. Thus, regardless of the extent of mismatch or the rate of stimulus presentation, the MMN will not be generated. This explanation assumes that the sensory memory comparison that is responsible for the MMN may still be functional during the sleep period. However, since information extracted from the standard and deviant is not available for the sensory memory comparison system, the MMN will not be elicited. There is good evidence that auditory sensory transmission is inhibited during

non-REM sleep by the thalamus (Coenen, 1998; Steriade, McCormick, & Sejnowski, 1993). In this and many other studies, N1, peaking at about 100 ms, is at or near baseline level in stage 2 and slow-wave sleep. Source dipoles for N1 are located in areas around the auditory cortex (Scherg & Picton, 1991). Thus input to the N1 cortical generators also appears to be inhibited during non-REM sleep. Loewy et al. (1996) have proposed that N1 might need to reach critical peak amplitude before the MMN can be generated.

The transition from a fully waking conscious state to one of sleep and unconsciousness is thus associated with a number of changes in the processing of human auditory information as measured by evoked potentials recorded from the scalp. The amplitude of a negative wave peaking at about 100 ms, N1, declines to near baseline level during stage 2 sleep. This N1 has been associated with a general or fuzzy type of consciousness. It may represent an awareness that a stimulus has been presented, but without knowledge of the specific features and classification of this stimulus. When a stimulus physically changes among a train of rapidly presented standard stimuli, the deviance has been hypothesized to be detected automatically prior to actual conscious recognition of the deviant. This preconscious detection of deviance is responsible for the occurrence of the Mismatch Negativity. The MMN may continue to be elicited until shortly after definitive sleep onset (stage 2 sleep), if the deviant stimulus is very discrepant relative to the standard. If the deviant is only slightly different from the standard, changes to the MMN occur as early as stage 1. In deeper sleep (stages 3 and 4) however, even the preconscious detection of very large and infrequent changes in the external environment cannot be made.

Figure Captions

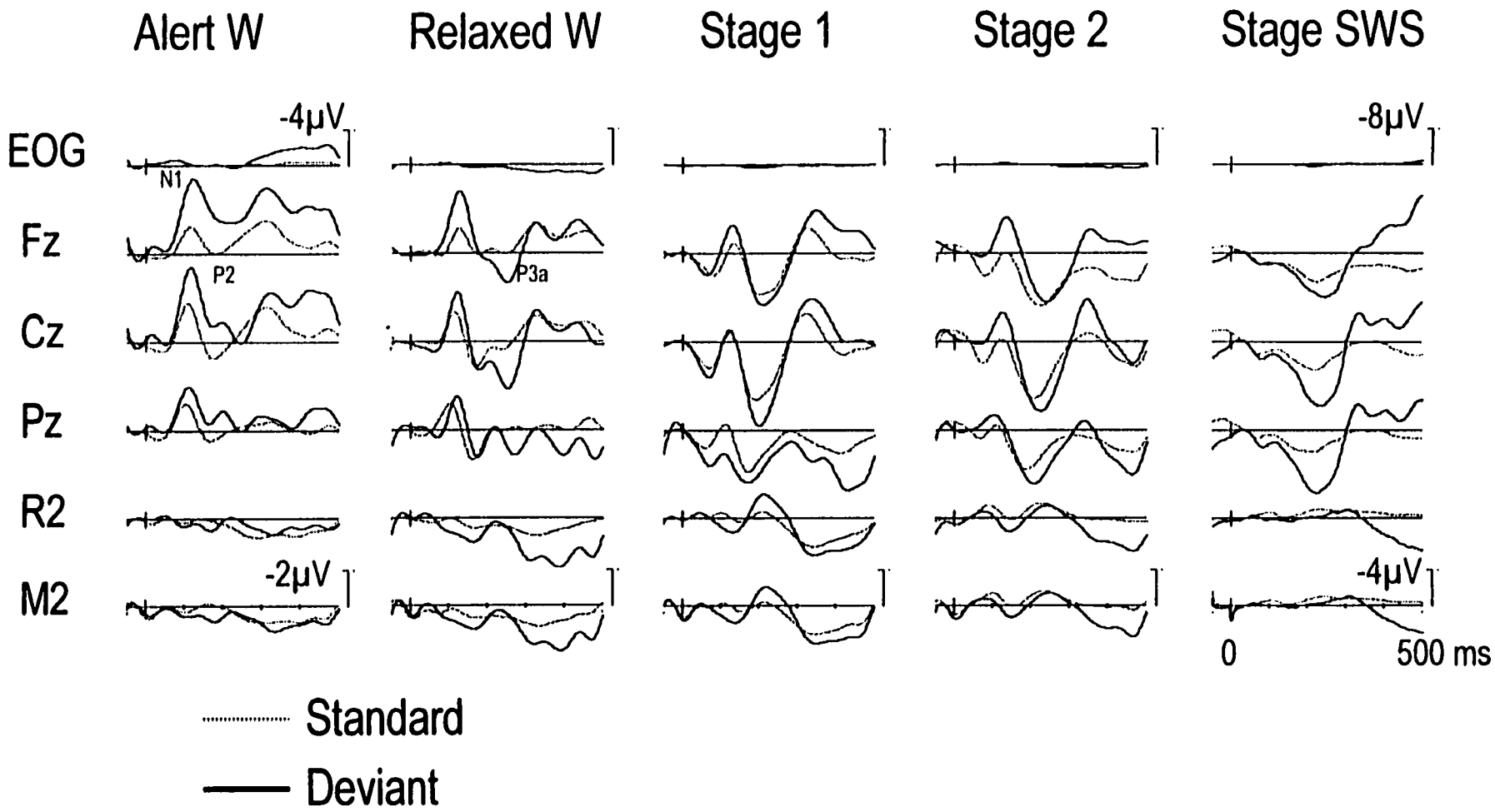
Figure 2.1. Grand-averaged waveforms following the standard (1000 Hz) and large deviant (2000 Hz) stimuli for midline (Fz, Cz, Pz, Oz), right mastoid (M2), and the mid-point between the right mastoid and Fz (R2) electrode sites. A negative peak, "N1" is visible at approximately 80-100 ms following the standard stimulus. N1 decreases in amplitude as the participant enters sleep (stages 1 and 2). The deviant elicits a long-lasting negativity that overlaps and summates to the N1. Note that in this and all other figures, waveforms are scaled at half amplitude during slow-wave sleep (SWS).

Figure 2.2. Grand-averaged large deviant difference waves for midline (Fz, Cz, Pz, Oz), right mastoid (M2), and the mid-point between the right mastoid and Fz (R2) electrode sites. . The difference waves were computed by subtracting the standard from the large deviant waveforms observed in Figure 1. A large and long-lasting negativity was elicited during alert wakefulness. This is the MMN. The early portion (100-150 ms) is still visible during relaxed wakefulness and at sleep onset in stages 1 and 2, although the later negativity (150-250 ms) is not. A positivity peaking at 255 ms is visible during relaxed wakefulness.

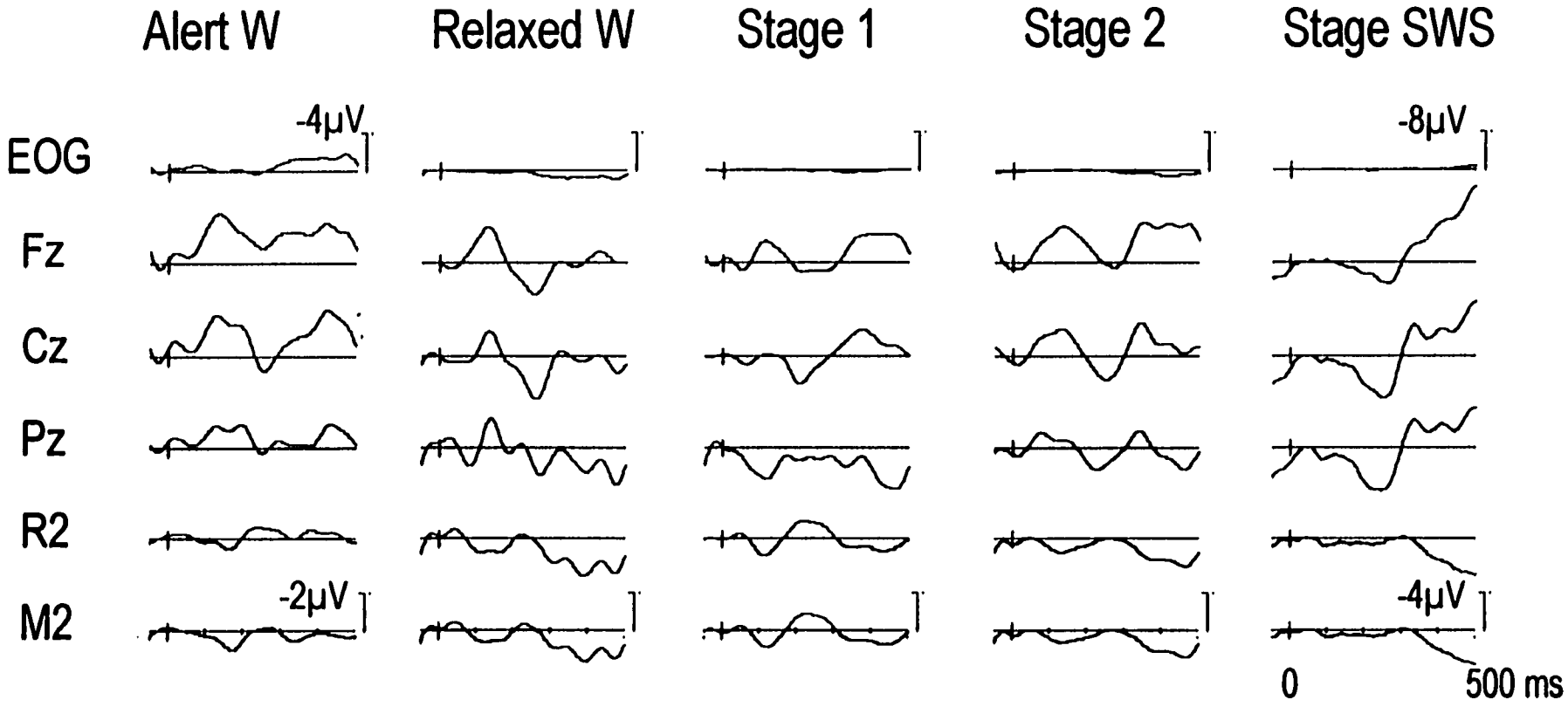
Figure 2.3. Grand-averaged waveforms following the standard (1000 Hz) and small deviant (1100 Hz) stimuli. The N1 is again visible during wakefulness and stage 1 but is at baseline level in stage 2 and slow-wave sleep.

Figure 2.4. Grand-averaged small deviant difference waves. The MMN is reduced in the alert wakefulness condition compared to when a large deviant was employed. No short latency (100-150 ms) MMN is visible in either relaxed wakefulness or at sleep onset.

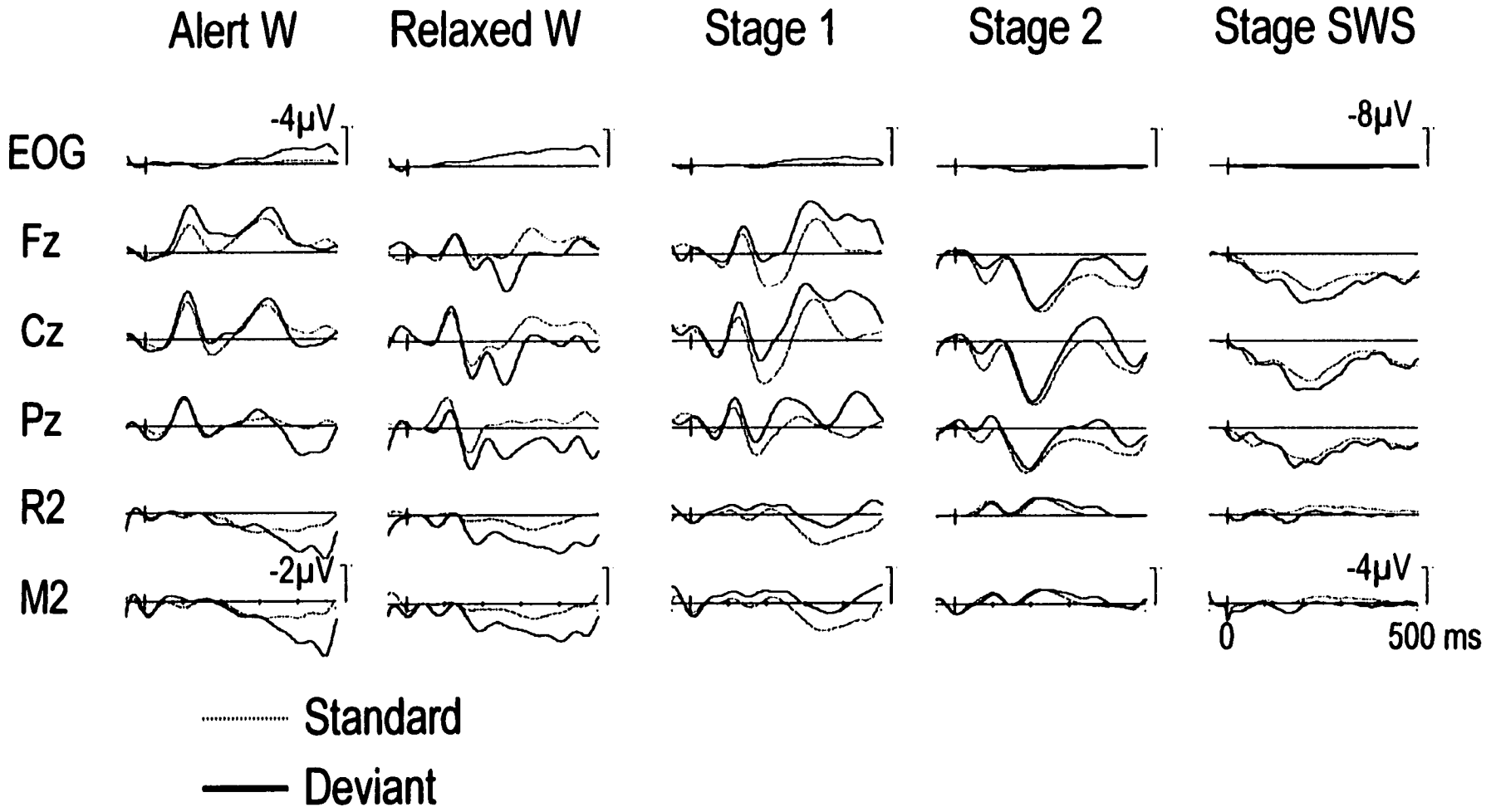
LARGE DEVIANT



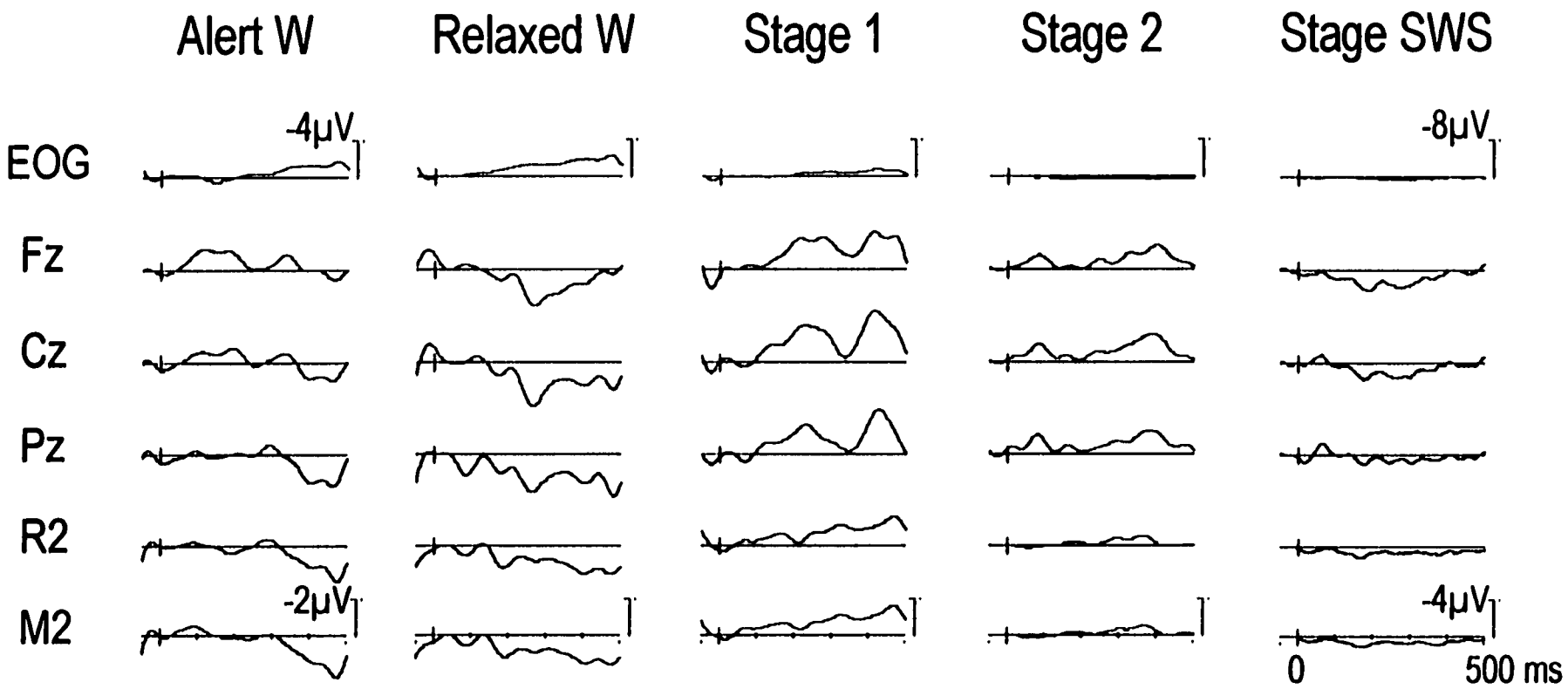
DIFFERENCE (Large Deviant - Standard)



SMALL DEVIANT



DIFFERENCE (Small Deviant - Standard)



Chapter 3

Experiment 2: Effects of Sequential and Temporal Probability of Deviant Occurrence on Mismatch Negativity

The following manuscript is "in press" in the journal *Cognitive Brain Research*. The mismatch negativity (MMN) increases in amplitude as the probability of deviant occurrence decreases. It is unclear whether the determining variable is sequential probability (i.e., the probability of a deviant within a number of standards) or temporal probability (i.e., the probability of a deviant within a period of time). Eleven subjects heard a train of frequently occurring 1000 Hz standard tones. The probability of a 1100 Hz pitch deviant was manipulated. In one condition the SOA was 150 ms, with temporal probability of deviant occurrence being either 1/9.00, 1/4.50, 1/2.25, or 1/1.125 s (sequential probability being 1/60, 1/30, 1/15 or 1(deviant)/7.5(standards), respectively). In another condition the SOA was 600 ms, with temporal probability being either 1/9.00, 1/4.50, or 1/2.25 s (sequential probability being 1/15, 1/7.5, 1/3.75, respectively). In a final condition, the SOA was 2400 ms with temporal probability being 1/9.00 s (sequential probability 1/3.75). Both sequential and temporal probabilities have a marked effect on the MMN. When a deviant occurred every 2.25, 4.50, and 9.00 s, the MMN increased as temporal probability decreased. When a deviant occurred every 7.5 or 15 standards, the MMN was larger for lower sequential probability, but the effect was not significant. Nevertheless, when temporal probability was held constant at 1/9.00 s, the MMN increased as sequential probability decreased. At rapid rates of stimulus presentation, the MMN was largest. However, it was attenuated when the probability of deviant occurrence was very

high perhaps due to the refractoriness of its generator. At the slowest rate, the MMN was diminished perhaps due to memory decay for the standard stimuli.

Introduction

The mismatch negativity (MMN) is an event-related potential (ERP) component that is elicited as a response to an infrequent "deviant" auditory stimulus occurring within a train of repetitive "standards" [13]. The MMN has been elicited by deviants that vary in tonal frequency [13,28], intensity [14], duration [17], spatial location [21], interstimulus interval [1,6,20], or complex stimuli properties, such as phonemes [26,34] or noise [23].

The MMN is thought to reflect a neural mismatch between the incoming deviant stimulus and the sensory memory representation already formed to the frequent standard stimuli [17,22]. Infrequent stimuli alone, without intervening standard stimuli, do not elicit the MMN [8,16]. According to the memory trace hypothesis, a MMN will be elicited as long as the neuronal representation of the standard stimulus still exists by the time the deviant stimulus is presented. The amplitude of the MMN varies inversely with the rate of stimulus presentation. When slow rates of stimulus presentation are employed, the amplitude of the MMN decreases since the memory trace created for the standard stimuli fades rapidly, before the presentation of the deviant. When fast rates are employed, the neuronal trace established for the repetitively presented standard tone is still active in sensory memory when the deviant is presented. The duration of the neuronal trace has been estimated to be between 2 and 4 s [11,15] (cf. [1]) using electrical recordings, about 10 s using magnetic recordings [27], and up to 20 s according to behavioral studies [2]. The variation in these estimates may stem from the different methodology used in the different studies (e.g., measurement techniques, stimulus parameters, task demands, SOA pattern) [22].

Another critical determinant of the MMN is the probability of occurrence of the deviant stimulus. The amplitude of MMN is inversely related to the probability of occurrence of the deviant. As the probability of deviant occurrence increases, the amplitude of the MMN decreases [12,19]. It is not clear, however, whether the determining factor is sequential probability (i.e., the probability of a deviant within a certain number of standards in a block of trials) or temporal probability (i.e., the probability of a deviant within a period of time in a block of trials). The majority of studies report the sequential probability of deviant occurrence, neglecting its temporal probability. When stimulus-onset-asynchrony (SOA) is held constant, manipulation of sequential probability will also alter temporal probability. For example, if the SOA is 600 ms and the sequential probability of deviant occurrence is 1(deviant)/15(standards), then the temporal probability of deviant occurrence is, on average, 1(deviant)/9.00 s. If sequential probability of deviant occurrence is changed to be 1(deviant)/7.5(standards), then its temporal probability becomes 1(deviant)/4.50 s. When sequential probability is held constant, the manipulation of SOA will alter temporal probability. Increasing the SOA (i.e., decreasing the rate of stimulus presentation) will decrease temporal probability. For example, if sequential probability is held constant at 1(deviant)/7.5(standards), increasing the SOA from 150 to 600 ms will decrease the temporal probability from 1(deviant)/1.125 to 1(deviant)/4.50 s, respectively. On the other hand, when temporal probability is held constant, manipulation of SOA will alter sequential probability. Increasing the SOA (i.e., decreasing the rate of stimulus presentation) will increase sequential probability. If temporal probability is held constant at 1(deviant)/9.00 s, increasing the SOA from 150 to 600 ms will increase the sequential probability from 1(deviant)/60(standards) to 1(deviant)/15(standards), respectively.

The independent effects of temporal probability, sequential probability and rate of stimulus presentation on the MMN have not been studied extensively. Näätänen et al. [15] compared the effect of temporal probability across different SOA conditions (varying from 51 to 4000 ms), when sequential probability of deviant occurrence was held constant at .10. In this study, MMNs were elicited in all conditions. The amplitude of the MMN did vary as a manipulation of temporal probability, but the effect was not significant. The effect of sequential probability (either .008, .017, or .05) was then compared across different SOAs (either 51, 101, or 301 ms) when temporal probability was held constant (approximately 1 deviant every 6 s). Under these conditions, the MMN was not different in amplitude for the different sequential probabilities. However, the MMN in the 51 ms SOA condition was significantly larger for the lower .008 compared to the .10 sequential probability. Similarly, the MMN in the 101 ms SOA condition was significantly larger for the lower .017 compared to the .10 sequential probability. Recently, Shelley, Silipo, and Javitt [29] examined the effects of sequential probability of deviant occurrence (varying from .25 to .025) on the amplitude of the MMN in schizophrenic and control participants, when the SOA was held constant at 250 ms. In line with the previous results, the authors found the MMN for controls to increase in amplitude as sequential probability (and thus temporal probability) of deviant occurrence decreased. However, only the MMNs to the highest and lowest sequential probabilities of deviant occurrence differed significantly (.25 and .025 respectively). In a second condition, temporal probability of deviant occurrence was manipulated by varying the SOA (either 250, 500, 1000, or 4000 ms) while sequential probability was held constant at .10. Consistent with Näätänen et al.'s [15] results, there was no significant difference in MMN amplitude as a function of temporal probability of deviant occurrence. Sussman, Ritter, and Vaughan [31] did find a significant effect of temporal

probability using very fast (100 ms) and slow (1300 ms) SOAs. The probability of deviant occurrence (.20) was unusually high. The MMN elicited in the slow SOA condition was considerably larger than that obtained in the fast SOA condition. The authors attributed the attenuation of the MMN in the fast SOA condition to the high temporal probability of deviant occurrence (1/.50 s). They suggested that the large MMN observed in the slow SOA condition might also be explained by a summation of the overlapping components N1 and MMN. Moreover, in this condition the standard and deviant stimuli were presented in a non-randomized predictable manner.

Unfortunately, studies that have attempted to examine the effects of sequential/temporal probability of deviant occurrence on MMN tend to employ a limited range of conditions. For example, sequential probability might be varied while holding a single temporal probability constant. Alternatively, temporal probability might be varied while holding a single sequential probability constant. There is good evidence that the rate of stimulus presentation will interact with both the effects of sequential and temporal probability [7]. For example, with slow rates of stimulus presentation the MMN might be attenuated due to weakening of the neuronal trace created by the standard tones. At very rapid rates of presentation the MMN might be attenuated due to the refractoriness of the MMN generator. The present study therefore examines the independent and interactive effects of both sequential and temporal probability on MMN generation when different rates of stimulus presentation are employed.

Methods

Participants

Eleven healthy university students (aged 18-26 years, 8 women) were paid an honorarium for their participation in the study. Subjects signed a consent form following an explanation of the nature of the experiment. This study was conducted following the ethical guidelines of the Medical Research Council of Canada.

Procedure

Subjects were seated in a sound-attenuated chamber and instructed to ignore the auditory stimuli by reading a self-selected book. Stimuli (80 dB SPL, 55 ms total duration having rise-and-fall of 5 ms) were presented binaurally through Eartone 3A insert earphones. The standard stimulus was a 1000 Hz and the deviant stimulus a 1100 Hz tone pip. The auditory stimuli were calibrated using a Bruel and Kjaer 2209 sound level meter, equipped with a 2 cm^3 acoustic coupler.

A total of eight different "oddball" stimulus conditions were tested. Both the stimulus-onset-asynchrony (SOA) and sequential probability were manipulated (see Figure 1). Three different SOAs were used. Stimuli were presented every 150, 600, or 2400 ms in different conditions. When the 150 ms SOA was used, the sequential probability of deviant occurrence was varied in four conditions (1/60, 1/30, 1/15, or 1(deviant)/7.5(standards), with temporal probability thus being either 1/9.00, 1/4.50, 1/2.25, 1(deviant)/1.125 s, respectively). When the 600 ms SOA was used, the sequential probability of deviant occurrence was varied in three conditions (1/15, 1/7.50, or 1(deviant)/3.75(standards)), with temporal probability thus being

either 1/9.00, 1/4.50, 1(deviant)/2.25 s, respectively). When the 2400 ms SOA was used, a single sequential probability of 1(deviant)/3.75(standards) was employed, the temporal probability thus being 1(deviant)/9.00 s. Within the 150 and 600 ms SOA conditions, an identical 1/9.00, 1/4.50, or 1(deviant)/2.25 s temporal probability was employed, while the sequential probability varied. The 1(deviant)/9.00 s temporal probability condition was also employed in the long 2400 ms SOA condition. Further, within the 150 and 600 ms SOA, an identical 1/7.5 and 1(deviant)/15(standards) sequential probability of deviant occurrence was varied. The order of presentation of the eight experimental conditions was randomized. The order of presentation of the different stimuli within each condition was randomized with the restriction that a minimum of three standard stimuli separated each deviant stimulus. Each condition lasted ten minutes, with a total of 4000, 1000, and 250 trials being presented in each of the 150, 600 and 2400 ms SOA conditions, respectively. The entire procedure was repeated a second time in order to assure replicability of results.

----------Insert Figure 1 about here----------

EEG recording

EEG activity was recorded from seven channels using tin cup electrodes placed on Fz, Cz, Pz, FC3, FC4, and the left and right mastoids. The nose served as a reference. A vertical EOG was recorded from electrodes placed at the supra- and infra-orbital ridges of the right eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. The ground electrode was placed on the forehead. Inter-electrode impedances were below 5 kΩ. Data were acquired continuously using a 256 Hz sampling rate. The high filter was set at 30 Hz. The time constant was 2 s. EOG artifact was corrected using an algorithm operating in the frequency domain. Trials in which the EEG exceeded ±100μV were rejected from further

analysis. The EEG signals were later reconstructed into discrete epochs beginning 100 ms prior to stimulus onset and continuing for 450 ms following it (i.e., a total sweep time of 550 ms). ERPs were subsequently digitally low-pass filtered using an inverse FFT algorithm with a 20-Hz high frequency cutoff.

Data measurement and statistical analysis

Difference waveforms were computed by subtracting, point-by-point, the standard from the deviant waveforms at each electrode site within a condition. The 450-ms post-stimulus period was subdivided into nine 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. The average of all data points in the 100 ms pre-stimulus period served as a baseline from which all interval amplitudes were measured. An initial analysis of the Fz data (where the MMN was largest) was performed to determine if the difference waveforms recorded in each of the conditions significantly varied from the zero amplitude pre-stimulus baseline. Confidence intervals were then computed for each of the nine latency intervals. This procedure is equivalent to computing a *t*-test between the standard and deviant waveforms [32]. To restrict the likelihood of a chance finding, the time window of occurrence and the scalp topography were constrained to conform to that observed in literature. The MMN had to occur within a 100-350 ms time window after stimulus onset and be larger frontally/centrally than parietally. In addition, a polarity inversion had to be observed at the mastoids. The design of the present experiment was not balanced. For this reason, separate analyses of variance (ANOVA) were performed. A one-way repeated measures ANOVA was performed to compare the effects of deviant probability of occurrence within the 150 ms SOA condition. A second one-way ANOVA was performed on the 600 ms SOA condition. Two separate two-way repeated

measures ANOVAs were performed to determine the effects of sequential and temporal probabilities for both time intervals. The first ANOVA consisted of two within factors, SOA (150, 600 ms) and temporal probability (1/9.00, 1/4.50, 1(deviant)/2.25 s). The second ANOVA also consisted of two within factors, SOA (150, 600 ms) and sequential probability (1/7.50, 1(devaint)/15(standards)). When the SOA was 2400 ms, temporal probability was 1 deviant on average every 9 s. This probability was also employed when SOAs were either 150 or 600 ms. A one-way repeated measures ANOVA was therefore used to compare the effects of sequential probability of deviant occurrence (1/3.75, 1/15, or 1(deviant)/60(standards)) when temporal probability was held constant at 1(deviant)/9.00 s. When a significant main effect was found, Newman-Keuls *post-hoc* comparisons (.05 criterion level) were used to determine significant difference among the different conditions.

Results

The grand average frontal (Fz) ERPs to standard and deviant stimuli when temporal probability is varied are presented in Figure 2. At the fast rate of stimulus presentation (every 150 ms), N1 was difficult to discern following the standard stimulus. N1 amplitude, however, was very large when stimuli were presented slowly in the 2400 ms SOA condition.

----------Insert Figure 2 about here----------

The grand average Fz difference waveforms for all conditions appear in Figure 3 and 4. The mean Fz amplitudes of the difference waveforms for each 50 ms interval appear in Table 1. A significant MMN was evident in all conditions ($p < .05$) except when the SOA was 2400 ms.

The deviant-standard difference was significantly negative-going in both the 100-150 and 150-200 ms time intervals ($p < .05$) in these conditions. These negativities showed a maximal frontocentral scalp distribution, a polarity reversal at the mastoids and were larger over the right hemisphere (FC4).

----------Insert Figures 3 and 4 about here----------

----------Insert Table 1 about here----------

The amplitude of the MMN in both the 150 and 600 ms SOA conditions increased as the probability (i.e., both temporal and sequential) of deviant occurrence decreased. When the SOA was 150 ms, a one-way ANOVA on the difference scores revealed a significant main effect of sequential/temporal probability in the 150-200 ms time interval, $F(3,30) = 4.11$, $p<.01$, $MS_e = 1.31$. Post-hoc testing indicated that the MMN in the 1(deviant)/60(standards) sequential probability (or 1(deviant)/9.00 s temporal probability) condition was significantly larger than the MMNs in the 1/7.5, 1/15 and 1(deviant)/30(standards) sequential probabilities (or 1/1.125, 1/2.25 and 1(deviant)/4.50 s temporal probability) conditions. All other differences were not significant ($P > .05$). When the SOA was 600 ms, a one-way ANOVA on the difference scores did not reveal a significant effect of sequential/temporal probability.

Effects of temporal probability

When the SOA was either 150 or 600 ms, the temporal probability of deviant occurrence was manipulated to be either 2.25, 4.50, or 9.00 s. These results are illustrated in Figures 2 and 3. The two-way ANOVA on the difference scores with SOA and temporal probability as factors revealed a significant main effect of the SOA within the 101-150 and 151-200 ms time intervals, $F(1,10) = 6.37$, $p<.05$, $MS_e = .61$ and $F(1,10) = 6.25$, $p<.05$, $MS_e = 1.56$, respectively. The MMN in the fast SOA (150 ms) conditions was significantly larger than that observed in the

intermediate SOA (600 ms) conditions. When the SOA is varied and temporal probability is constant, sequential probability will be altered accordingly. As sequential probability was lowered (by speeding the SOA), the amplitude of the MMN significantly increased. A significant main effect of temporal probability, $F(2,20) = 13.48$, $p<.01$, $MS_e = 1.52$ was also observed within the 101-150 and 151-200 ms time intervals. Post-hoc testing indicated that the MMN in the 151-200 ms time interval for 1/9.00 s temporal probability was significantly larger than the MMN for 1/4.50 s temporal probability, which, in turn, was significantly larger than the MMN for 1/2.25 s temporal probability. However, in the 101-150 ms time interval only MMNs to the highest and lowest temporal probabilities (1/2.25 compared to 1/9.00 s) differed significantly. There was no significant interaction between SOA and temporal probability, $F<1$.

Effect of sequential probability

When the SOA was either 150 or 600 ms, the sequential probability of deviant occurrence was manipulated to be either 1/7.5 or 1(deviant)/15(standards). These results are illustrated in Figure 4. The two-way ANOVA on the difference scores with SOA and sequential probability as factors revealed a significant main effect of SOA, but only within the 151-200 ms time interval, $F(1,10) = 6.34$, $p<.05$, $MS_e = 1.09$. The MMN in the intermediate SOA (600 ms) conditions was significantly larger than that observed in the fast SOA (150 ms) conditions. In the intermediate 600 ms conditions, the temporal probability of deviant occurrence was lower than in the fast 150 ms conditions. Thus, as temporal probability is decreased, when identical sequential probabilities are employed, the amplitude of the MMN significantly increases. There was no effect of sequential probability for any time interval ($F(1,10) = 1.29, 1.42$, $p>.05$, $MS_e = .92, 1.19$, for the 101-150 and 151-200 time intervals, respectively). There was no significant interaction between SOA and sequential probability, $F<1$.

The one-way ANOVA on the difference scores, when temporal probability was held constant at 1/9.00 s, revealed a significant main effect of SOA within the 100-150 ms time interval, $F(2,20) = 8.29$, $p<.01$, $MS_e = 1.13$. Post hoc testing indicated that the MMN during the 150 ms SOA condition was significantly larger than the MMN during the 600 ms SOA condition, which, in turn, was significantly larger than the MMN during the 2400 ms SOA condition.

Discussion

The SOA had a large effect on the amplitude of the standard and deviant waveforms. As the rate of stimulus presentation increased, the amplitude of N1 following the standard became markedly attenuated. It is likely that at such fast rates of presentation the N1 generator is either refractory or actively inhibited due to habituation [10]. At the slowest rate of stimulus presentation (every 2400 ms), the N1 amplitude was very large. The N1-P2 complex was prominent in both standard and deviant waves due to the long SOA [18]. Both elicited a P3a component that could be related to an involuntary attention switching to infrequent salient stimuli [30].

The MMN was also markedly affected by the rate of stimulus presentation, but in a manner opposite to that of N1 [11,27]. The MMN was visible when stimuli were presented rapidly but was not significantly different from pre-stimulus amplitude when stimuli were presented slowly (every 2400 ms). Many studies have now indicated that the amplitude of the MMN becomes markedly attenuated when stimuli are presented quite slowly. The MMN is viewed as an automatic deviance detection system. A comparator detects a mismatch between

the memory trace to repetitive, homogeneous standard stimuli and the physical attributes of a deviant stimulus. The MMN can be elicited only if the neuronal representation of the standard still exists at the moment when the deviant occurs. If the rate of stimulus presentation exceeds several seconds, the memory for the standard stimuli will gradually decay [11]. According to the memory decay account, repetitions of the standard stimuli guard its memory presentation from fading. Alternatively, a slow rate of presentation places the deviant out of context and hence the MMN is reduced [3]. According to this account, the standard acts as a norm and the longer the SOA, the more distant the deviant is from the train of standards, which makes it out of context. A somewhat similar explanation postulates that the deviance detection system uses the temporal pattern in which stimuli appear as a predictor of the following stimulus [4,33]. The system is then set for a specific stimulus, but slow rates of presentation weaken its prediction potential. Evidence supporting the involvement of memory traces in MMN generation comes mainly from studies in which a masking stimulus either follows (backward masking) or precedes (forward masking) both standard and deviant [12]. In these studies, short SOAs (<150 ms) produce strong masking effects and a diminished MMN.

When the standard stimuli were presented rapidly (either 150 or 600 ms), large amplitude MMNs were observed following presentation of the deviant when it occurred very infrequently (on average, every 9 s). However, when standards were presented slowly (every 2400 ms), only a small, non-significant MMN-like wave could be observed following the deviant, even though it also occurred on average, every 9 s. Other studies have also found that the amplitude of the electrical MMN is much attenuated when the SOA exceeds 2 s, although the effect is not always significant [11,15]. Thus, the rate of stimulus presentation interacts with the rarity of deviant occurrence to influence the amplitude of the MMN. It is possible that the use of especially low

temporal probability in the current study might explain our result. Further systematic investigation that controls for the different parameters employed is needed in order to determine the SOAs in which MMN can no longer be elicited.

The MMN will then be attenuated if stimuli are presented slowly. However, the MMN can also be attenuated when stimuli are presented rapidly, if the probability of deviant occurrence is particularly high. At the fastest rate of stimulus presentation (every 150 ms), the amplitude of the MMN decreased as the sequential/temporal probability of deviant occurrence increased. When a deviant occurred every 1.125 s, only a small MMN could be observed. A memory trace might be formed by the deviant stimuli when these are presented in close succession [25]. This memory representation could still be in an active state when the subsequent deviant is presented. The amplitude of the MMN in these conditions will thus be reduced because of the refractory period of the MMN generator. The high occurrence of the deviant stimulus appears to put the deviance detection system in "confusion" as the set [4,33] or the context [3] is changed frequently.

Consistent with previous studies, the amplitude of the MMN increased as the sequential/temporal probability of deviant occurrence decreased (e.g., [19]). This effect, however, was found to be significant only during the fast SOA (150 ms) condition. During the intermediate SOA (600 ms) condition, the MMNs were not significantly different for the probabilities tested. The effects observed for the fast SOA were mainly due to the very low 1/30, 1/60 sequential probabilities. These probabilities were not employed during the 600 ms SOA conditions. Excluding these probabilities from the 150 ms SOA analysis eliminated the significant effect. Interestingly, the amplitude of the MMN was largest when combining the fastest SOA with the lowest sequential probability of deviant occurrence.

Effects of temporal probability

When the SOA was either 150 or 600 ms, a significant main effect of temporal probability was found when a deviant occurred on average every 2.25, 4.50, and 9.00 s. Again, as temporal probability (and thus sequential probability) of deviant occurrence decreased, the amplitude of the MMN increased. In this analysis, the MMN during the fast SOA (150 ms) was significantly larger than that observed in the intermediate SOA (600 ms) conditions. The rate of stimulus presentation determines the number of repetitions of the standard stimulus for a given probability (sequential or temporal), which may affect the strength of the memory trace that is formed by the standard. When the rate of presentation is fast, the standard is repeated frequently creating an especially strong memory trace. Alternatively, at the fast rate of presentation the memory trace has not had sufficient time to fade, or misplace its norm. When the rate of presentation is slow, the memory for the standard is weaker since a fewer number of standards have been presented. Alternatively, it is possible that at slow rates, the memory trace begins to fade, or the deviant is out of context.

Effects of sequential probability

When temporal probability was held constant at 1/9.00 s, the MMN increased as sequential probability decreased. Näätänen et al. [15] did note that the MMN varied with sequential probability, but the effect was not significant. In their study, temporal probability was held constant at 1/6.00 s and the SOAs were relatively fast (51, 101, 301 ms). In the present study, a wider time gap between the slowest and fastest SOA was used in order to accommodate a wider range of sequential/temporal probability of deviant occurrence.

On the other hand, there was no significant main effect of sequential probability when a deviant occurred on average, every 7.5 or 15 standards. In these conditions, however, only a

limited range of sequential probabilities was employed. This is consistent with Näätänen et al.'s [15] findings that the effects of sequential probability will only be manifested when a wider range of probabilities is used. The 1/7.5 and 1/15 probabilities of deviant occurrence might therefore have not been sufficiently wide apart to elicit significant MMN differences.

In this analysis, the MMN during the intermediate SOA (600 ms) was larger than that observed during the fast SOA (150 ms) conditions. This result is opposite to the trend found when sequential probability was varied. This apparent contradiction may be explained by the unbalanced design of the study. When a fast 150 ms SOA was employed, in some conditions the deviant occurred very infrequently. Thus if the time interval between deviants is especially long, the MMN generator would be active (not in its refractory period), resulting in a large amplitude MMN. However, if the time interval between deviants is especially short, the MMN generator may be refractory. When the analysis was limited to the 1/7.5 and 1/15 sequential probabilities during the 150 and 600 ms SOA conditions, deviants occurred more rapidly in the 150 ms SOA condition. Thus, the reduction of the MMN during the 150 ms SOA conditions might be explained by refractoriness of MMN generator rather than a main effect of the SOA.

In summary, our findings illustrate that both sequential and temporal probability of deviant occurrence have a marked effect on the MMN. For a constant sequential probability, MMN is larger for lower temporal probability. For a constant temporal probability, MMN is larger for lower sequential probability. These results are consistent with the view that the two factors affect the same process either in one stage or in parallel stages. Both determine the status of the memory trace of the standard or the standard as the norm stimulus in a given context. This implies that a single mechanism may compute how often a deviant occurs relative to the standard and how often a deviant occurs in time. The memory trace is a prerequisite for activating the

deviance detection system underlying the MMN [35]. In order for change detection to occur the standard must be in an active state, and be well-established in memory or as a norm. When long SOAs are employed, there is the possibility of either a memory decay for the standard or alternatively a change in context since a previous norm is no longer applicable.

In most oddball paradigms, sequential probability of deviant occurrence is usually about 1/7.5 or 1(deviant)/15(standards). Our findings suggest that in these studies, temporal probability (as will be determined by the SOA) plays a major role in determining the generation of the MMN. This is especially relevant in experiments in which the MMN elicited is much attenuated even though traditional stimulus parameters have been employed. For example, the MMN is difficult to elicit during sleep [9,24], coma [5], or with clinical populations [29]. It is possible that the absence of an MMN in such studies is due to the fact the deviants may be presented too frequently in time. In order to maximize the likelihood of MMN elicitation standard stimuli should be presented relatively rapidly while deviants should occur quite rarely. Unfortunately, in some cases such optimization might be difficult or impossible to achieve due to practical limitations in the duration of testing (i.e., the lower the temporal probability, the longer the testing duration). Moreover, when deviants occur rarely the resulting averaged evoked potentials may remain noisy due to an insufficient number of trials having been presented (the lower the temporal probability, the lower the number of deviants available for averaging).

Table 3.1
Mean amplitudes (μV) and standard deviations (parentheses) of the difference waveforms at Fz for each 50 ms interval of the total 450 ms sweep

Condition	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
SOA = 150 ms Temp. Prob.= 1/1.125 s Seq. Prob.= 1/7.5	-0.01 (0.56)	-0.12 (0.41)	-0.72* (0.58)	-0.78* (0.58)	-0.70* (0.70)	-0.81* (0.70)	-0.81* (0.60)	-0.83* (0.67)	-0.75 (0.72)
[a]SOA = 150 ms Temp. Prob.= 1/2.25 s Seq. Prob.= 1/15	-0.24 (0.62)	-0.07 (0.70)	-1.07* (0.79)	-1.09* (1.45)	-0.72 (1.19)	-0.40 (0.83)	-0.41 (1.03)	-0.41 (1.31)	-0.47 (1.21)
SOA = 150 ms Temp. Prob.= 1/4.50 s Seq. Prob.= 1/30	-0.13 (0.62)	-0.13 (0.94)	-1.36* (1.28)	-1.71* (1.30)	-1.13* (1.77)	-0.97 (1.82)	-0.56 (1.84)	-0.49 (1.65)	-0.59 (1.56)
[b]SOA = 150 ms Temp. Prob.= 1/9.00 s Seq. Prob.= 1/60	-0.43 (1.15)	-0.40 (0.99)	-2.13* (1.33)	-3.38* (2.46)	-1.12* (1.32)	0.03 (1.95)	-0.10 (1.72)	-0.62 (1.86)	-0.82 (1.19)
SOA = 600 ms Temp. Prob.= 1/2.25 s Seq. Prob.= 1/3.75	-0.29 (0.66)	-0.51* (0.69)	-0.50 (1.11)	-0.41 (1.37)	-0.04 (1.29)	0.54 (1.12)	0.74 (1.08)	0.51 (1.34)	0.37 (1.50)
[a]SOA = 600 ms Temp. Prob.= 1/4.50 s Seq. Prob.= 1/7.5	-0.01 (0.97)	-0.54 (1.09)	-1.16* (1.75)	-1.49* (1.84)	-0.11 (3.21)	0.90 (2.51)	0.32 (2.55)	0.24 (2.31)	0.14 (2.35)
SOA = 600 ms Temp. Prob.= 1/9.00 s Seq. Prob.= 1/15	-0.10 (0.96)	-0.06 (0.75)	-1.46* (1.50)	-1.97* (1.64)	-0.51 (1.95)	0.27 (1.60)	0.42 (1.60)	-0.23 (1.75)	-0.93 (1.25)
SOA = 2400 ms Temp. Prob.= 1/9.00 s Seq. Prob.= 1/3.75	0.35 (1.08)	0.15 (0.81)	-0.31 (1.41)	0.21 (2.57)	0.98 (2.04)	1.14 (2.39)	1.49 (3.06)	0.94 (2.65)	1.05 (2.36)

For all conditions n=11, except for [a] where n=10 and [b] where n=8.
* Negative amplitude values significantly different from the baseline ($p < .05$).

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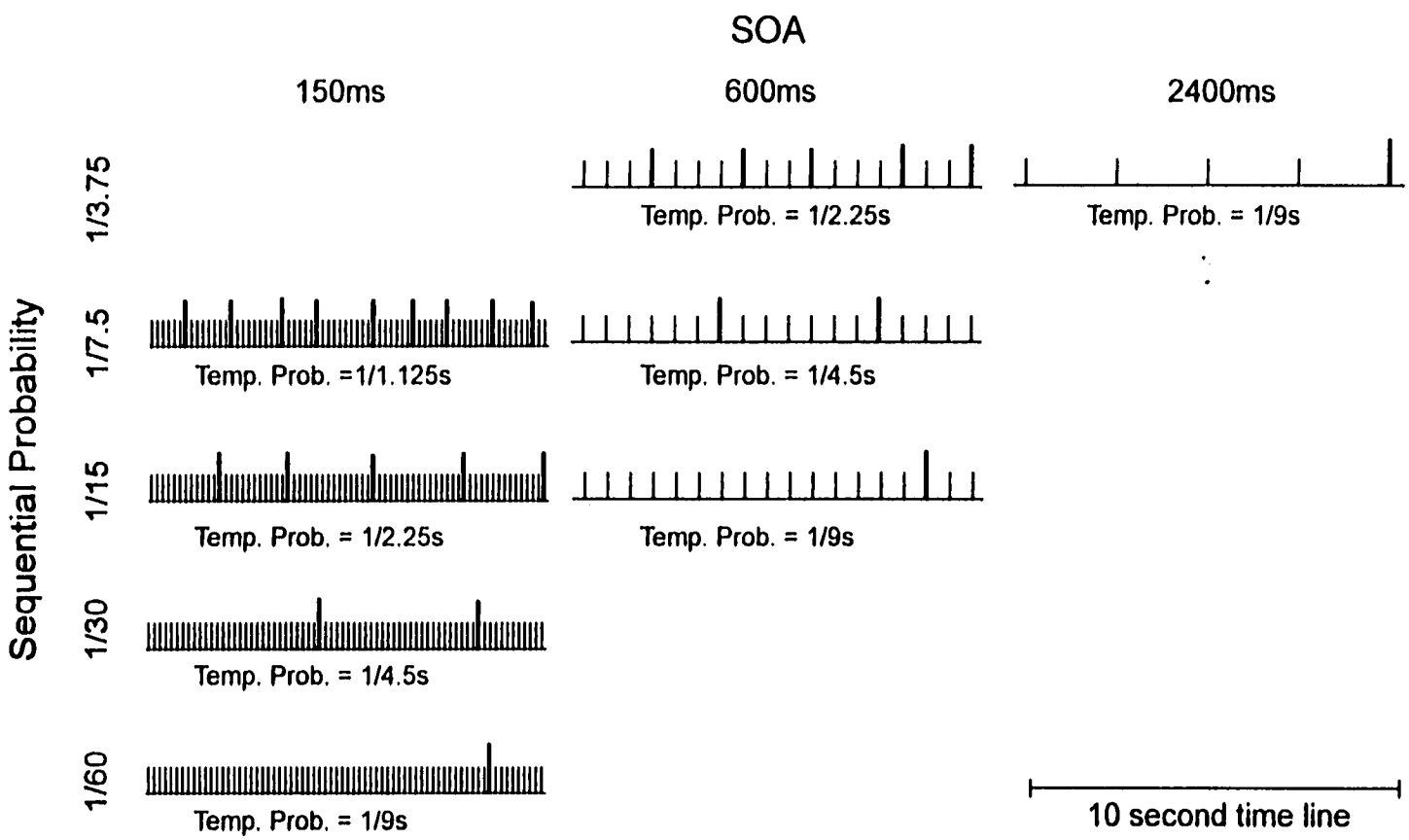
Figure Legends

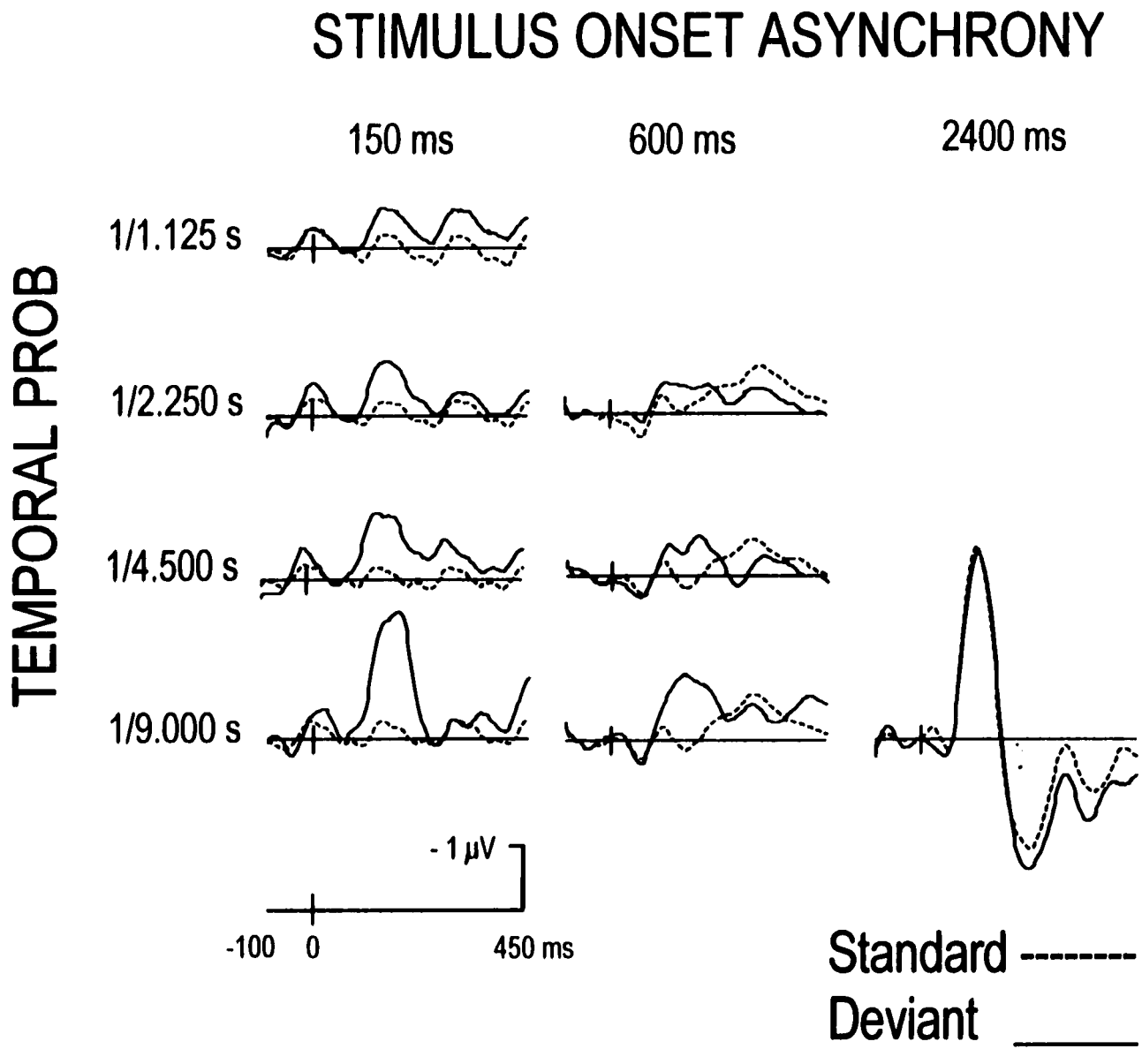
Figure 3.1. Schematic diagram of the eight conditions used to dissociate temporal from sequential probability effects. Long markers represent the deviant stimuli and short markers the standard stimuli.

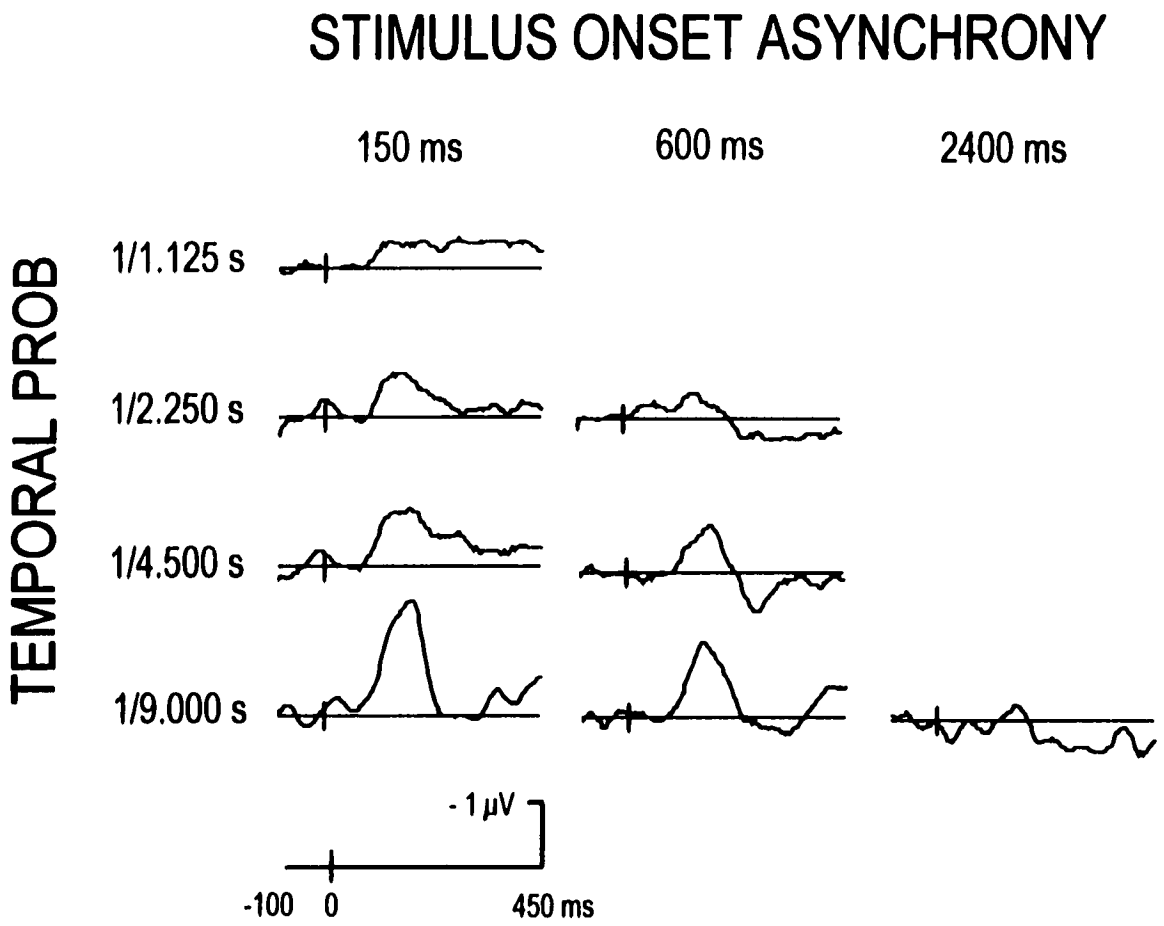
Figure 3.2. Grand average frontal (Fz) waveforms following the standard (1000 Hz) and the deviant (1100 Hz) for all conditions, when temporal probability is varied.

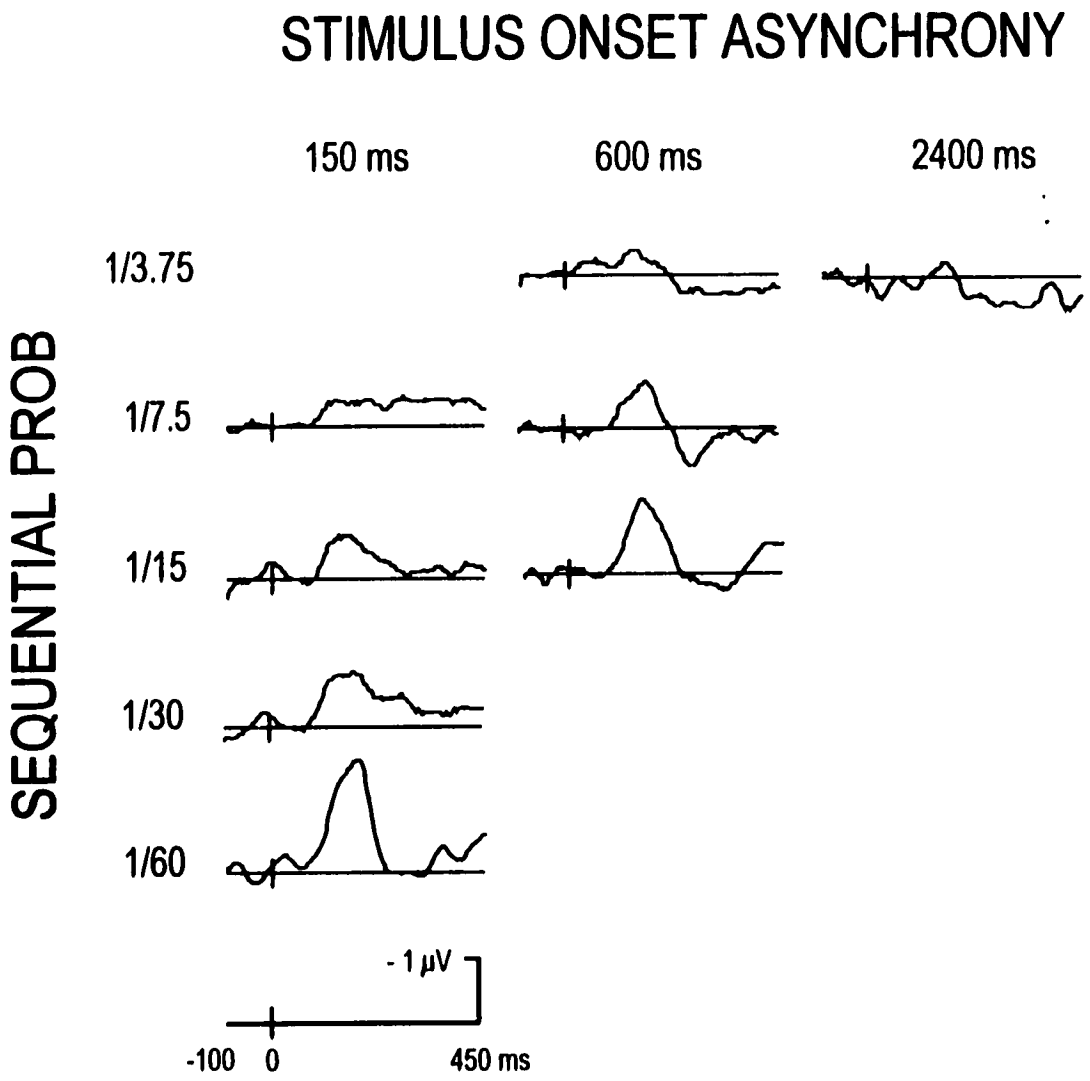
Figure 3.3. Grand average Fz difference waves for all conditions, when temporal probability is varied.

Figure 3.4. Grand average Fz difference waves for all conditions, when sequential probability is varied.


SOA
150ms
600ms
2400ms
Sequential Probability
1/3.75
1/7.5
1/15
1/30
1/60
Temp. Prob. = 1/2.25s
Temp. Prob. = 1/9s
Temp. Prob. =1/1.125s
Temp. Prob. = 1/4.5s
Temp. Prob. = 1/2.25s
Temp. Prob. = 1/9s
Temp. Prob. = 1/4.5s
Temp. Prob. = 1/9s
10 second time line


STIMULUS ONSET ASYNCHRONY
150 ms
600 ms
2400 ms
TEMPORAL PROB
1/1.125 s
1/2.250 s
1/4.500 s
1/9.000 s
- 1 µV
-100
0
450 ms
Standard -------
Deviant _____


STIMULUS ONSET ASYNCHRONY
150 ms
600 ms
2400 ms
TEMPORAL PROB
1/1.125 s
1/2.250 s
1/4.500 s
1/9.000 s
- 1 μV
-100
0
450 ms


STIMULUS ONSET ASYNCHRONY
150 ms
600 ms
2400 ms
SEQUENTIAL PROB
1/3.75
1/7.5
1/15
1/30
1/60
- 1 μV
-100
0
450 ms

Chapter 4

Experiment 3: Effects of loss of consciousness on the MMN to frequency deviants using a rapid rate of presentation

This manuscript has been submitted to the journal *Psychophysiology*. The present study examines the effects of sleep onset -- the transition from a waking, conscious state to one of sleep and unconsciousness -- on the mismatch negativity (MMN) following frequency deviants when a rapid rate of stimulus presentation is employed. A 1000 Hz standard stimulus was presented every 150 ms. At random, on 6.6% of the trials, the standard was changed to either a large 2000 or a small 1100 Hz deviant. During alert wakefulness (when subject ignored the stimuli and read a book), the large deviant elicited a larger MMN than the small. The MMN continued to be elicited following the large deviant in relaxed wakefulness (eyes closed) and Stages 1 and 2 of sleep although it was reduced in amplitude. Fewer trials were presented during slow-wave sleep, dominated by high amplitude background EEG. In spite of the noisy waveform, a significant MMN was also elicited in slow-wave sleep. A significant MMN was recorded for the small deviant only in alert wakefulness. No significant MMN was observed in relaxed wakefulness or in any stage of sleep. These results support the hypothesis that the MMN comparison system is at least partially automatic. It can be elicited during non-REM sleep, at least for very large frequency deviance. It is possible that during sleep onset cortical encoding of both the standard and deviant is weakened because of prior thalamic inhibition of sensory input.

Introduction

A fundamental role of the nervous system is to detect change in the environment. A response of the brain, labeled the Mismatch Negativity (MMN), appears to serve as a change or deviance detector. The response can be elicited in the so-called oddball paradigm. A subject is presented with a deviant auditory stimulus occurring infrequently in a sequence of otherwise repetitive, homogeneous standard auditory stimuli (Näätänen, Gaillard, & Mäntysalo, 1978). The MMN is observed as a negative event-related potential (ERP) wave to the deviant stimulus relative to the standard stimulus. The MMN is maximum over fronto-central areas of the scalp and inverts in polarity at the mastoids when the nose is used as the reference (Alho, Paavilainen, Reinikainen, Sams, & Näätänen, 1986). It overlaps with the N1-P2-N2 wave complex, beginning as early as 50 ms after deviant onset, and lasting up to 300 ms. The MMN component can be elicited by a variety of auditory stimulus changes, including tonal frequency (Näätänen et al., 1978; Sams, Paavilainen, Alho, & Näätänen, 1985), intensity (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987a; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993), duration (Näätänen, Paavilainen, & Reinikainen, 1989; Novak, Ritter, Vaughan, & Wiznitzer, 1992), interstimulus interval (Böttcher-Gandor & Ullsperger, 1992; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1987b) and complex stimulus features such as phonemes (Rinne, Alho, Alku, Holi, Sinkkonen, Virtanen, Bertrand, & Näätänen, 1999) or noise (Muller-Gass, Marcoux, Logan, Campbell, 2001; Sabri & Campbell, 2000).

The MMN component is commonly viewed as an operational index of an automatic deviance detection system. A comparator notes a mismatch between a sensory memory representation of the standard stimulus and the physical attributes of the incoming deviant

stimulus (Näätänen, 1992). Importantly, infrequent tones alone, without intervening standard tones, do not elicit the MMN (Korzyukov, Alho, Kujala, Gumenyuk, Ilmoniemi, Virtanen, Kropotov, & Näätänen, 1999; Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989). Moreover, the component can be elicited only if the sensory memory representation of the standard still exists when the deviant occurs. Sensory memory fades rapidly especially for unattended stimuli (Cowan, Lichty, & Grove, 1990). Thus, when slow rates of stimulus presentation are employed, the MMN is attenuated since the sensory memory for the standard has already faded by the time the deviant is presented. By contrast, rapid repetitions of the standard stimulus guard it from degrading in memory, ensuring that the representation is still active when the deviant is presented. The duration of this sensory memory has been estimated to last between 2 and 4 s using electrical recordings (Mäntysalo & Näätänen, 1987; Näätänen et al., 1987b; Sabri & Campbell, in press; cf. Böttcher-Gandor & Ullsperger, 1992), 10 s using magnetic recordings (Sams, Hari, Rif, & Knuutila, 1993), and up to 20 s according to behavioral studies (Cowan, 1984).

The MMN is usually recorded when the subjects' attention is directed away from the stimuli by engaging them in a primary task such as reading a book. The methodology is based on the assumption that the MMN is automatic, independent of attention, and operational at a pre-conscious level of processing (Näätänen & Gaillard, 1983; Näätänen et al., 1993; Näätänen & Winkler, 1999; Sams et al., 1985). The MMN appears to be relatively robust to attentional manipulations. Nevertheless, its amplitude to small frequency deviants (Alain & Woods, 1997; Alho, Woods, Algazi, & Näätänen, 1992; Otten, Alain, & Picton, 2000; Trejo, Ryan-Jones, & Kramer, 1995; Woods, Alho, & Algazi, 1992) or to intensity deviants (Woldorff, Hackley, & Hillyard, 1991; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998) has been found to be

modulated by highly focused attentional manipulations, such as those employed in dichotic listening or bimodal selective attention tasks. Under these conditions, ignored deviants elicit an attenuated MMN relative to attended deviants. Attending to a deviant, though, may result in the elicitation of an additional negativity peaking at about 250 ms, the N2b, which can overlap with the MMN. It is not clear, therefore, if the enhancement of the MMN in attend conditions is due to the MMN itself or to the summating effects of the overlapping N2b. The N2b is associated with an attentional switch and is usually followed by a later frontal positivity peaking at about 250-300 ms, the P3a (Näätänen, 1992; Schröger, 1996). When the magnitude of physical difference between the standard and the deviant is large and/or the deviant is very intrusive, the N2b-P3a complex can be elicited even when the deviant is ignored (Sams et al., 1985; Sasaki, Campbell, Bazana, & Stelmack, 2000).

An alternative approach for evaluating the presumed automaticity (i.e., attention independence) of the MMN is to record it during unconscious states, such as sleep or coma. If the MMN reflects preconscious processing of the deviant stimulus it should be observable during sleep. The MMN to frequency deviants or complex auditory pattern has been reported to occur in rapid-eye movement (REM) sleep, although its amplitude is much reduced relative to waking states (Atienza & Cantero, 2001; Atienza, Cantero, & Gómez, 1997, 2000; Loewy, Campbell, & Bastien, 1996). On the other hand, MMN to intensity deviants has not been observed during REM sleep (Loewy, Campbell, de Lugt, Elton, & Kok, 2000).

The consensus emerging from studies of non-REM (NREM) stages of sleep is different. Almost all of studies have failed to observe an MMN in NREM sleep to either frequency deviants (Loewy et al., 1996; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Nittono, Momose, & Hori, 2001; Paavilainen, Cammann, Alho, Reinikainen, Sams, & Näätänen, 1987;

Sallinen, Kaartinen, & Lyytinen, 1994; Winter, Kok, Kenemans, & Elton, 1995) or intensity deviants (Loewy et al., 2000). Sallinen et al. (1994) did report an MMN following frequency deviants in Stage 2 sleep, but only when the deviant stimulus also elicited a K-Complex. A problem with this study is that the K-Complex consists of at least two very large amplitude negative components beginning at about 300 ms following stimulus onset. It is thus difficult to dissociate the overlapping temporal and spatial aspects of the actual K-Complex negativities from a true MMN.

The loss of consciousness is thus associated with an inability to elicit the MMN. Recently, Sabri, de Lugt, & Campbell, (2000) studied the MMN to frequency deviants during the critical sleep onset period, the transition from a waking, conscious state to one of sleep and unconsciousness. A standard 1000 Hz tone was presented on 80% of the trials and on the remaining 20% of the trials, either a large (2000 Hz) or a small (1100 Hz) deviant tone was presented at random. A stimulus was presented every 600 ms. During alert wakefulness, subjects read a book, thus ignoring the tones. Subjects were then permitted to sleep and testing continued throughout the sleep onset period and included relaxed wakefulness (awake with eyes closed) and Stages 1 and 2 of sleep. The duration of the transitional Stage 1 period can be very short. For this reason, at least five onset periods were obtained for each subject in order to accumulate a sufficient number of trials during Stage 1 to permit averaging. Trials which included a K-Complex were removed from ERP analysis. Sabri et al. found a small MMN to be elicited during Stage 2 sleep, but only after presentation of the large 2000 Hz deviant. The MMN could not be observed in sleep following the small 1100 Hz deviant.

In a very recent study, Nittono et al. (2001) also attempted to record the MMN at sleep onset. The auditory stimuli were 1000 Hz standard ($p=.90$), 1200 Hz large deviant ($p=.05$), and

1050 Hz small deviant (p=.05). Two sleep onsets and definitive sleep were recorded over two different nights. Stimuli were presented every 500 ms. The authors categorized the sleep onset period into a series of sub-stages using a method developed by Hori and colleagues (Hori, Hayashi, & Morikawa, 1994). The MMN following either deviant was elicited in EEG Stages I (epoch including alpha waves >20μV) and II (Stage 1, suppressed alpha waves <20μV). Consistent with Sabri et al. (2000), the MMN was not discernable in EEG Stages III (Stage 1, low-voltage theta waves), IV (Stage 1, vertex sharp waves), and V (Stage 2, at least one sleep spindle).

Two possibilities have been proposed for the failure to elicit a definitive MMN during NREM sleep. In the first account, the failure to elicit the MMN may be due to the inhibition of stimulus input prior to entry into the cortical sensory memory comparison system (Campbell, 2000; Sabri et al., 2000). Sleep is known to be associated with thalamic gating of sensory input into the cerebral cortex (Coenen, 1998; Steriade, McCormick, & Sejnowski, 1993). During NREM sleep, cerebral blood flow is globally reduced as compared with both waking and REM sleep states (Braun, Balkin, Wesensten, Gwadry, Carson, Varga, Baldwin, Belenky, & Herscovitch, 1998; Maquet, Péters, Aerts, Delfiore, Degueldre, Luxen, & Franck, 1996). Neural activity is depressed in many regions including the prefrontal cortex, thalamus, the reticular activating system, and basal ganglia. However, sensory areas, such as the auditory cortex, including the MMN generator of the supratemporal plane (e.g., Levänen, Ahonen, Hari, McEvoy, & Sams, 1996; Scherg, Vajsar, & Picton, 1989), remain active (Maquet, Degueldre, Delfiore, Aerts, Péters, Luxen, & Franck, 1997). Thus, NREM sleep may degrade input to the MMN generators but has little direct effect on the activity of the actual generators.

In the second account, NREM sleep may affect the rate at which neural representations

fade from sensory memory. In waking adults, sensory memory persists from 2 to 10 s. The duration of the memory trace may however be much shorter in NREM sleep. The failure to observe an MMN during NREM sleep may thus be due to the relatively slow rate of stimulus presentation employed in sleep studies. In these studies, the rate of stimulus presentation ranges from 510 (Paavilainen et al., 1987) to 1000 ms (Winter et al., 1995). It is possible then that, during NREM sleep, even the fastest rate of presentation is too slow to maintain the sensory memory trace. Thus, in spite of the fact that the MMN generators remain active in NREM sleep, rapid memory decay of the standard neuronal representation prevents detection of the deviant.

In the present study, a very rapid rate of stimulus presentation is employed. Thus, the neural representation of the standard should still be active upon presentation of the deviant, even within NREM sleep. We again examined the changes in the MMN during the transition from a fully awake and conscious state to one of unconsciousness and NREM sleep. The occurrence of the MMN in NREM sleep would support the hypothesis that the sensory memory trace for the standard stimulus remains active. By contrast, failure to observe the MMN during NREM sleep would be consistent with the hypothesis that sensory input has already been degraded prior to entry into the cortical MMN comparison system.

Method

Subjects

Twelve (7 men, and 5 women) healthy, right-handed undergraduate university students volunteered to participate in this study. Subjects were between the ages of 18 and 27 (mean = 23.2 years). All were self-reported good sleepers with no history of hearing or neurological

disorders. Subjects were instructed to refrain from alcohol and caffeine use within 24 hours of testing. Prior to testing, informed consent was obtained from each subject. All subjects received an honorarium for their participation in the study. This study was conducted following the tri-council (natural, health, and social science) Canadian ethical guidelines.

ERP recordings

The electroencephalogram (EEG) and electrooculogram (EOG) were recorded using Grass gold-cup electrodes. They were filled with electrolytic paste, and affixed to the skin by surgical tape and to the scalp by gauze. The EEG was recorded from five scalp locations placed at midline frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) sites, and from the right mastoid (M2). The reference was the tip of the nose. A vertical EOG was recorded from electrodes placed at the supra- and infra-orbital ridges of the right eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. Blinks, vertical eye movements and saccadic eye movements (associated with reading, while the subject was awake) could easily be distinguished from the horizontal slow eye movements that appeared in Stage 1 sleep. A ground electrode was placed on the forehead. Inter-electrode impedances were kept below 5 kΩ. The filter bandpass of the analogue amplifiers was from 0.16 to 35 Hz.

The EEG and EOG data were digitized at a 256 Hz sampling rate, using a 12-bit analogue-to-digital (A/D) converter and stored continuously to hard disk. Off-line, the continuous data were reconstructed into discrete trials or "sweeps". A sweep began 50 ms prior to stimulus onset and continued for another 450 ms following it (i.e., the total sweep time was 500 ms). The averaged waveforms for each condition were subsequently digitally filtered using an inverse FFT algorithm with a bandwidth of 3-20 Hz (3 dB roll-off). The 3 Hz low filter setting is unusually high for most MMN studies. It is, however, consistent with other studies investigating the

effects of unconscious states on information processing (Loewy et al., 1996, 2000; Sabri et al., 2000). The purpose of the low filter setting was to attenuate the effects of large slow delta activity occurring in NREM sleep. Also, sleep is known to remove a long-lasting negativity that overlaps and summates with the MMN (Campbell, 2000; Campbell, Bell, & Bastien, 1992). The low filter will attenuate this effect.

Stimuli

Evoked potentials were elicited using standard 1000 Hz tone pips (80 dB SPL; 55 ms total duration; 5 ms rise/fall time). Two different infrequently occurring deviant stimuli were employed. The pitch of a large deviant was 2000 Hz while that of a small deviant was 1100 Hz. The auditory stimuli were synthesized using a 16-bit waveform generator card. Stimulus probability was 0.934 for the standard stimuli and 0.033 for each of the two deviant stimuli. Standard and deviant stimuli occurred pseudorandomly with the restriction that two deviants could not be presented consecutively. Stimuli were presented at a constant stimulus-onset asynchrony (SOA) of 150 ms. A deviant was therefore presented, on average, every 4.5 s. A total of 5000 trials was presented per block. All auditory stimuli were presented monaurally to the left ear via Eartone 3A insert earphones. A Bruel and Kjaer 2209 sound level meter equipped with a 2 cm^3 coupler was used to calibrate the auditory signals.

Procedure

Subjects were instructed to arrive at the laboratory approximately 2 hours before their normal bedtime. At that time, electrodes were affixed and baseline testing took place. Testing began during the waking state. Subjects were instructed to read a self-chosen book while ignoring the tones (alert wakefulness condition). This condition was repeated four times (i.e., a total of 20,000 trials). The EOG was monitored to ensure that subjects continued reading. Upon

completion of the alert wakefulness condition, the lights were turned off and the subjects were allowed to fall asleep. Testing continued throughout the sleep onset period and included relaxed wakefulness (eyes closed), and Stages 1 and 2 of sleep. Some subjects also entered Stages 3 and 4 of sleep within a block of trials. The duration of Stage 1 varies widely among sleepers. It can last less than one minute or up to several minutes. The amplitude of the background EEG can be very large during sleep. The amplitude of the MMN is very small relative to the large amplitude ongoing EEG. Averaging of trials during a single Stage 1 period will not sufficiently attenuate the background EEG to permit observation of the MMN. In order to maximize the amount of data collected during the short sleep onset period, each subject was awakened repeatedly. At least ten onset periods were obtained for each subject. To verify that the subject was awake, he or she was asked a simple question. Once the subject was awakened and had correctly answered the simple question, he or she was then allowed to resume sleep at which time stimulus presentation began again. If the subject did not enter Stage 2 sleep, the entire block of trials was repeated. The ERP data were stored for further analyses only if the transition from wakefulness to sleep was captured within a block of trials. A total of at least 50,000 trials was presented during the sleep onset periods per subject (i.e., 46,700 standards, 1650 large and 1650 small deviants).

Data scoring and analysis

The different stages of sleep were classified by an experienced scorer according to the standard criteria of Rechtschaffen and Kales (1968). An epoch of 10 s was used for sleep staging rather than the usual 30 s in order to increase the precision of the scoring. In cases of stage ambiguity, the epoch was excluded from further analysis. ERPs were sorted into five different sleep/wake stages: alert wakefulness (awake while reading), relaxed wakefulness (lights out,

awake with eyes closed), Stage 1 sleep, Stage 2 sleep, and SWS (combined Stages 3 and 4 sleep). During the sleep onset period, relaxed wakefulness was defined by a predominance (> 50%) of low voltage alpha EEG activity and occasional rapid eye movements. Stage 1 sleep was defined by a loss of alpha (< 50%), a predominance of relatively low theta EEG activity, and the presence of slow rolling eye movements. Stage 2 was defined by the presence of sleep spindles and/or K-Complexes in a background of relatively low theta EEG activity. Stage 3 was defined by 25 to 50% of high amplitude slow delta wave activity. Stage 4 was defined by a minimum of 50% of high delta activity (Rechtschaffen & Kales, 1968). Stages 3 and 4 were combined and labeled as slow-wave sleep (SWS).

Trials in which the EEG or EOG exceeded ±100μV were rejected from further analysis during wakefulness or Stage 1 sleep. Unusually large amplitude eye movements (typically saccades while reading) or eye blinks occurring within the 500 ms sweep time would thus be rejected during the waking state. Similarly, large-amplitude, slow horizontal eye movements occurring within the sweep in Stage 1 sleep would also result in rejection of trials. However, this was a relatively rare occurrence. While large amplitude slow horizontal eye movements are common during Stage 1 sleep, the rejection criteria required that they occur during the 500 ms sweep time and that their amplitude exceed ±100μV. Single trial data in Stage 2, 3 or 4 sleep were rejected if either the EEG or EOG amplitude exceeded ±150μV (to permit inclusion of high amplitude delta waves).

Single trial ERPs were sorted and averaged within each sleep/wake stage. Separate averages were computed for the standard and deviant stimuli. The data were then collapsed across all sleep onset periods. The MMN is best observed in a subtraction waveform. The difference waveforms were computed by subtracting, point-by-point, the standard from the deviant

waveforms at each electrode site within each sleep/wake stage. The 400 ms post-stimulus sweep period was subdivided into eight 50 ms latency intervals starting at stimulus onset. (The last 50 ms of the sweep was not available due to distortion of the waveform introduced by the windowing function on the inverse FFT digital filter.) Within each of these intervals, the average of all data points was computed, yielding an average amplitude measure. The average of all data points in the 50 ms pre-stimulus period served as a zero amplitude baseline from which all amplitudes were measured. Confidence intervals were then computed for each of the eight latency intervals in order to evaluate whether the frontal (Fz) mean amplitudes of all subjects for each interval significantly differed from zero baseline. This procedure is equivalent to computing a t-test between the standard and deviant waveforms (Winer, 1971). All differences were considered significant at $p<.05$. The frontal electrode was chosen for the analyses because the MMN is largest at this site. To restrict the likelihood of a chance finding, the time window of occurrence and the scalp topography were constrained to conform to that observed in literature. The MMN had to occur only within a 100-250 ms time window after stimulus onset and be larger frontally/centrally than parietally. In addition, a polarity inversion had to be observed at the mastoid (M2). Once the existence of a MMN was determined within the different stages of sleep and wakefulness, a one-way repeated measures ANOVA was used to compare the effects of Stage on the MMN. When a significant main effect was found, Newman-Keuls post-hoc comparisons (.05 criterion level) were used to determine significant difference among the different conditions.

Results

The mean sleep onset latencies, defined as the delay from the start of stimulus presentation to the onset of Stage 1 sleep, ranged from an average of 215 s during the first sleep onset period to an average of 50 s during the last sleep onset period (i.e., tenth, eleventh, or twelfth). The mean sleep onset latency across all ten onsets was 95 s. There was no significant difference across onset periods. It should, however, be noted that these fast sleep onset latencies were confounded by the experimental paradigm. The data were analyzed only when a full transition from wakefulness to Stage 2 sleep occurred. If the subject did not fall asleep during the presentation of the 5000 stimuli, the data were rejected from further analysis. The mean number of averaged standard trials per subject within the alert wakefulness, relaxed wakefulness, Stage 1, Stage 2, and SWS conditions was 17936, 12254, 8345, 23403, and 5084, respectively.

Large deviance

The grand-averaged waveforms to the standard and large deviant stimuli in the different waking and sleeping states, using the 0.16 Hz low analogue filter, are superimposed in Figure 1. The data were smoothed using a 20 Hz high digital filter. The amplitude of N1 following the standard stimulus was very small, because of the rapid rate of presentation. It tended to be near or at baseline level in both the waking and sleeping states. On the other hand, the amplitude of N1 and P2 following the deviant stimulus was markedly affected by sleep onset and sleep. The deviant N1 gradually decreased in amplitude from alert wakefulness to Stage 2 of sleep. During SWS, it was below baseline. Similarly, the amplitude of P2 gradually increased in amplitude from alert wakefulness to SWS. The decrease in amplitude of N1 and the increase in amplitude of P2 during sleep onset are consistent with the removal of a long-lasting negative wave

occurring in the waking, conscious state. This positive shift may have overlapped and summated with the MMN. A significant MMN was observed in alert wakefulness and relaxed wakefulness within the 50-200 ms period, and in Stage 1 within the 100-150 ms interval.

----------Insert Figure 1 about here---------

In order to attenuate the effects of this long-lasting positive DC shift during sleep, a 3 Hz low digital filter was applied to the data. As may be observed in Figure 2, this filter had a marked effect on the morphology of the deviant while only slightly affecting the standard waveforms. In the alert wakefulness condition (while the subject read a book), a distinctive N1-P2 wave was observed following both standard and deviant stimuli. The deviant N1 and P2 peaked at 125 and 220 ms, respectively. The amplitudes of N1 and P2 following the deviant were –3.2 and 1.9μV, respectively. During Stages 1, 2, and SWS, the deviant N1 was recorded as a negative potential attaining approximately 70% of its waking amplitude and peaking about 10 ms later.

----------Insert Figure 2 about here---------

The grand-averaged difference waveforms for large deviants in the different waking and sleeping conditions are superimposed in Figure 3. The mean frontal amplitudes of the difference waveforms for each of the 50 ms interval in all states are presented in Table 1. When subjects were awake and alert, a long-lasting negative difference waveform was visible. This frontal MMN was significant in both the 100-150 and 150-200 ms intervals. The mastoid (M2) showed a polarity inversion across both intervals.

----------Insert Figure 3 and Table 1 about here---------

During relaxed wakefulness, the frontal MMN in the 100-150 and 150-200 ms intervals remained statistically significant. The MMN observed in Stage 1 was significant only in the

100-150 ms window. Within Stage 2, the long-lasting MMN was significant within the 50-200 ms period. A one-way ANOVA on these difference scores in the 100-150 ms time interval revealed a significant main effect of Stage, $F(3.33)=3.82$, $p<.02$, $MSE=.91$. Post hoc testing indicated that the MMN in the alert wakefulness condition was significantly larger than the MMNs in relaxed wakefulness and Stages 1 and 2. Differences among relaxed wakefulness and Stages 1 and 2 were not significant ($p>.05$).

Fewer deviants were presented in SWS (on average, 169 per subject) because subjects entered this stage toward the end of stimulus presentation, shortly before they were awakened. Also, the amplitude of the background EEG is very high during the delta-dominant SWS. The signal-to-noise ratio was thus lower in SWS compared with the other stages of sleep. A long-lasting, statistically significant negativity was, however, observed from 50 to 200 ms. The mastoid showed a polarity inversion. Nevertheless, this negativity appeared to begin slightly before or at stimulus onset. For this reason, the SWS data were not included in the ANOVA.

A centro-frontal positive wave peaking at 250 ms, perhaps a P3a, was observed following the deviant stimulus in the alert wakefulness, relaxed wakefulness, and Stage 1. It was also observed in Stage 2 and SWS, peaking at about 270 ms. However, it was not significantly different from baseline level. The MMN was followed by a late negative wave, peaking on average at 350 ms. It was significantly different from baseline level in both waking and sleeping states. This late negativity was largest at the central site. There were, however, no significant differences across the various waking and sleeping states ($F>1$).

Small deviance

The grand-averaged waveforms to the standard and small deviant stimuli in the different waking and sleeping states, using the 0.16 Hz low analogue filter, are superimposed in Figure 4.

These data were smoothed using a 20 Hz high digital filter. N1 was much larger following the deviant stimulus. The amplitude of N1 following the standard stimulus was near baseline level in both the waking and sleeping states. The amplitudes of N1 and P2 following the deviant stimulus were markedly attenuated to near baseline level during the transition from alert wakefulness to relaxed wakefulness and Stages 1 and 2. During SWS, the deviant waveform appeared as a sustained negative wave. A significant long-lasting MMN was observed in alert wakefulness within the 50-400 ms period and in relaxed wakefulness within the 100-200 ms period. No MMN was recorded in Stages 1, 2 and SWS.

----------Insert Figure 4 about here---------

A 3 Hz low digital filter was also applied to these data. The results are presented in Figure 5. In the alert wakefulness condition, a clear N1-P2 wave was observed following both standard and deviant stimuli. The deviant N1 and P2 peaked at 146 and 231 ms, respectively. The amplitude of N1 and P2 following the deviant was −1.0 and 0.2 μV, respectively. During Stages 1, 2, and SWS, the deviant N1 was recorded as a negative potential attaining approximately 40% of its waking amplitude and peaking about 20 ms later.

----------Insert Figure 5 about here---------

The grand-averaged difference waveforms in the different waking and sleeping states are superimposed in Figure 6. The mean frontal amplitudes of the difference waveforms of the small deviant for each 50 ms interval in all states are presented in Table 2. When subjects were awake and alert, a small but significant frontal MMN was evident in the difference waves in both the 100-150, and 150-200 ms intervals, respectively. This MMN peaked at a later interval (i.e., 150-200 ms) and was significantly reduced in amplitude compared with the MMN following the large deviant. The mastoid (M2) showed a polarity reversal.

----------Insert Figure 6 and Table 2 about here---------

Within relaxed wakefulness and Stage 1 and 2, very small negativities were measured. These were not statistically significant. A long-lasting negativity from 50 to 450 ms was observed during SWS. However, this negativity began prior to stimulus onset and showed no polarity reversal at the mastoid. Thus, the deviant waveform was considered to be largely residual noise following averaging.

P3a was not identified in any condition. The MMN in the alert wakefulness condition was followed by a significant negativity in the 350-400 ms period. This late negativity was not observed in either relaxed wakefulness or in any stage of sleep.

Discussion

Most studies report that the MMN is difficult to elicit in unconscious states, such as NREM and coma. When the EEG shows signs of cortical arousal, such as in REM sleep or during the emergence from coma, an MMN begins to appear (Atienza & Cantero, 2001; Atienza et al., 1997, 2000; Fischer, Morlet, Bouchet, Luaute, Jourdan, & Salord, 1999; Kane, Curry, Butler, & Cummins, 1993; Kane, Curry, Rowlands, Manara, Lewis, Moss, Cummins, & Butler, 1996; Loewy et al., 1996). The purpose of the present study was to examine the presumed pre-attentive, automatic MMN response during the transition from a fully aroused and conscious state to one of low arousal and unconsciousness. The sleep onset period provides a crucial means to test the effects of loss of consciousness/attention on the MMN.

Näätänen (1990, 1992) has claimed that the MMN reflects the outcome of a comparison process automatically registering the deviation of the current input from the neuronal

representation of a repetitive stimulus in sensory memory. Generation of the MMN depends on sensory representation that preserves information about the repeated standard stimulus. For MMN to be elicited in response to a stimulus change, this representation must be both well established as a standard in memory, and in currently active state (Cowan, Winkler, Teder, & Näätänen, 1993). This requires that the standard be adequately encoded, subsequently stored and active in sensory memory. Repetitions of the standard stimulus are required in order to sustain its representation active in memory and postpone the inevitable decay over time (Ritter, Deacon, Gomes, Javitt, & Vaughan, 1995).

Sleep and attention could affect either perceptual, sensory encoding and/or memory retention of the standard (Cowan, 1995; Cowan et al., 1990). NREM sleep is characterized by a very marked inhibition of input into the cortex (Coenen, 1998), probably occurring in the reticular-thalamic system (Steriade et al., 1993). Thus, in the first account, the failure to observe the MMN during NREM sleep might be explained by inadequate sensory input and consequently poor encoding of the standard and deviant stimuli. In the second account, the neuronal encoding of the standard is thought to be adequate, but the duration of sensory memory for the standard is unusually brief. Sensory memory would thus be postulated to fade much more rapidly in sleep as compared to wakefulness. To test these two opposing hypotheses, in the present study stimuli were presented very rapidly. Rapid rates of stimulus presentation help to preserve memory for the standard. Thus, upon presentation of the deviant, its trace can be compared to that of the still active, well-established standard representation. The MMN should therefore be elicited if, in fact, the standard and deviant have been effectively encoded in the temporal cortex during NREM sleep.

The difference waveform obtained in alert wakefulness for both small and large deviants conformed to that reported in the literature. The MMN was largest at fronto-central sites, occurred within the MMN time window, and showed a polarity reversal at the mastoid site. The MMN following the large deviant was larger in amplitude and shorter in latency compared to that of the small deviant. The large deviant waveform was associated with a later central-maximum positivity, perhaps the P3a. However, this positivity was very small and did not reach significance. When a 3 Hz low digital filter was applied to the data, an MMN-like wave became apparent during relaxed wakefulness, Stage 1, 2 and SWS, but only to the large frequency deviance. The large deviant MMNs elicited in relaxed wakefulness, Stage 1 and 2 had similar peak latencies, but were significantly attenuated relative to alert wakefulness. There was no significant difference between the MMNs elicited in relaxed wakefulness, Stages 1 and 2. Only a very small MMN was observed following the small deviant in relaxed wakefulness and NREM sleep. These negativities were, however, not significantly different from baseline level. Both large and small deviants were followed by a late negativity peaking at about 350 ms in the alert wakefulness condition, and in relaxed wakefulness and sleep following the large deviant.

The present results are similar to those observed in our previous sleep onset study (Sabri et al., 2000). An attenuated MMN was observed in relaxed wakefulness and Stage 2 sleep following the large deviant. In the Sabri et al. (2000) study, a significant MMN could not be observed in either Stage 1 or SWS. Since fewer trials were presented in these stages, it was suggested that background noise levels might not have been sufficiently reduced to allow identification of the low amplitude MMN signal. In the present study, the number of trials presented was greatly increased through additional repetitions of sleep onsets, and the MMN was found to be significant. Moreover, deviants were presented much more rarely (on average, every

30 trials) compared to the previous study (on average, every 10 trials). Nevertheless, the temporal probability of deviant occurrence was approximately similar in both studies (on average, every 4.5 in the present study compared to every 6.0 s) as rates of presentation were 150 and 600 ms, respectively. At these rates of stimulus presentation, Sabri and Campbell (in press) have indicated that the major determinant of MMN amplitude is temporal probability of occurrence of the deviant. Thus, differences in the sequential probability of deviant occurrence between the two studies cannot account for the different results.

The Sabri et al. (2000) study failed to observe MMNs in either relaxed wakefulness or sleep following the small deviant (1100Hz). They, however, presented stimuli relativity slowly (every 600 ms), and employed only half the number of sleep onset periods compared to the present study. Nittono et al. (2001) also could not observe the MMN when subjects entered Stage 1, dominated by either theta activity or vertex sharp waves, or Stage 2 of sleep. However, stimuli were again presented relatively slowly (every 500 ms). Also, only two sleep onset periods were used, limiting the number of trials available for averaging three sub-divisions of Stage 1. In the present study, a small but nonsignificant MMN was apparent in relaxed wakefulness and NREM sleep. Thus, as subjects became drowsy and entered sleep the small frequency deviance could not elicit the MMN. These results are in accord with the MMN susceptibility to attentional manipulations, when the magnitude of deviance is small (Alho et al., 1992; Woods et al., 1992). Therefore, only very large frequency changes appear to be able to elicit the MMN during NREM sleep. This is, however, problematic for the interpretation of the MMN. A deviant that is physically quite distinct from the standard may also result in an enhancement of N1 itself. N1 increases in amplitude as the rate of stimulus presentation is slowed (Näätänen & Picton, 1987). In the present study, the time interval between standards was

very short. This explains why N1 was much reduced in amplitude following the standards. On the other hand, the time interval between deviants was much longer (on average, every 4.5 s). Thus, it is possible that the increased negativity following the large deviant was due to an enhancement of N1 (Näätänen et al., 1987b). When a large deviant is employed, the MMN occurs temporally at about the same time as N1. It is thus difficult to separate the overlapping effects of N1 and the MMN. Unfortunately, it would appear that only very large stimulus changes may elicit MMN-like waves in NREM sleep.

There are other methodological difficulties that are encountered in the sleeping state. The sleep onset period is marked by an increasing amount of slow-wave, high amplitude delta activity. The high amplitude background noise will require many additional stimuli to be presented in order to detect the small amplitude MMN. The amplitude of delta activity can however be attenuated through judicious use of filter algorithms. Care must, however, be exercised not to also filter the signal of interest, the MMN.

Also, as already mentioned, significant changes occur to the N1-P2-N2 vertex potential which overlaps with the MMN. Näätänen, Gaillard, and Mäntysalo (1978, 1980) noted that in wakefulness when stimuli are attended the N1-P2 waveform is overlapped by a long-lasting negative-going wave, the processing negativity (PN). The PN is considered to reflect the extent of additional processing that an attended channel receives. As such, N1 amplitude is larger and P2 amplitude smaller in the attended compared to unattended channels. However, the to-be-ignored channels cannot be completely ignored. Subjects in the waking state almost always report some conscious awareness of the to-be-ignored stimuli. For this reason, Campbell et al. (1992) suggested that in alert and awake subjects all stimuli will elicit at least some PN, even if the stimuli are to be ignored. In the present alert wakefulness condition, subjects ignored the

auditory stimuli while reading a book. However, because they were unlikely to be able to completely ignore the auditory stimuli, a PN was probably elicited. A characteristic of sleep onset is that subjects gradually lose consciousness of the external environment. Information processing of all but the most relevant of stimuli is inhibited during NREM sleep in order to protect the sleeper from unwanted disturbances and awakenings. This massive inhibition of stimulus input is associated with the removal of the long-lasting PN. Its removal is observed in the evoked potential waveform by a marked attenuation of N1 that approaches the zero baseline level. The removal of PN has an opposite effect on P2. Because sleep removes an overlapping negative wave, P2 may increase in amplitude.

The PN is larger for stimuli that are presented infrequently since stimuli that occur rarely are difficult to ignore (Schwent, Hillyard, & Galambos, 1976). Thus, the PN was larger for the infrequently occurring deviants than for the frequently occurring standards. The deviant, however, also elicits the MMN. The low 3 Hz digital filter was applied in order to attenuate the overlapping effects of the PN. In the waking state, the filter had minimal effects on the MMN whereas in the sleep onset, it had a very large effect. The negativity that is associated with the PN is removed by the sleep inhibitory system. The removal of this negativity (i.e., increase in positivity) will summate to the negative-going MMN and might have effectively cancelled it out. The 3 Hz low filter, however, may serve to attenuate the overlapping and summating effects of the removal of the long-lasting slow PN, thus allowing the MMN to be observed. The use of a relatively high low filter setting is common in study of unconscious states (Fischer et al., 1999; Kane et al., 1996; Loewy et al., 1996, 2000; Sabri et al., 2000; Sallinen et al., 1994; Sallinen & Lyytinen, 1997). The 3 Hz low filter had minimal effects on the MMN in the waking state. Unlike the case in the present study, several authors (Fischer et al., 1999; Loewy et al., 1996,

2000; Sabri et al., 2000) have also claimed that a 3 Hz filter has a minimal effect on the MMN during unconscious states. Nevertheless, the use of any filter involves a methodological compromise. There is always the risk that both the background noise (delta activity and the PN) and the signal of interest (the MMN) will be attenuated when the frequency spectrum of the two sources overlap.

In agreement with other studies (Atienza et al., 2000; Loewy et al., 1996; Nittono et al., 2001; Sabri et al., 2000), a later significant negativity was observed within the 300-450 ms period following both large and small deviants in the alert wakefulness condition. This late negativity might represent what Schröger and Wolff (1998) call a re-orientation negativity (RON) following a deviant that is distinctly different from the standard. Because this type of deviant is obtrusive, the subject needs to become refocused (or re-oriented) to the primary task, reading a book. Consistent with the RON, the late negativity was maximum over central areas of the scalp. The RON, however, does not occur in ignore conditions (Schröger, Giard, & Wolff, 2000) such as that employed in the alert wakefulness condition. This negative wave might be a confound caused by the rate of stimulus presentation. A standard was always presented 150 ms following the occurrence of a deviant. It is possible that the standard also elicited an MMN as it failed to match the previous stimulus, the deviant. If true, the MMN would occur at about 150-200 or at 300-350 ms after the previous deviant. It is unlikely that the late negativity is a result of the MMN. The MMN is maximum over frontal areas of the scalp while as already mentioned the late negativity observed in alert wakefulness had a vertex maximum scalp distribution.

During sleep onset, a similar vertex maximum negativity occurring at about 350 ms was also observed. Sleep onset is associated with an apparently unique waveform, labeled the N350. The amplitude of the N350 was much larger than that observed in alert wakefulness. Colrain, Di

Parsia, and Gora (2000) have carefully monitored the development of the N350 (labeled N300 in their study) during the sleep onset period. N300 could not be elicited by a rare deviant stimulus in the waking state. However, their stimuli were presented very slowly. During Stage 1, dominated by alpha activity, N300 could still not be observed. However, when Stage 1 was dominated by theta activity, a vertex-maximum N300 emerged and it became larger in amplitude during Stage 2 sleep. Thus, in their paradigm the N300 appears to occur only within sleep. Colrain, Webster, Hirst, & Campbell (2000) employed a 32 channel EEG recording to map the N350 response. The stimulus (either a rare auditory deviant or an occlusion of breathing) elicited different types of waveforms. The stimulus could elicit a K-Complex, dominated by a very large amplitude negative wave peaking at 550 ms. However, the K-Complex also elicited an earlier N350. Often, the stimuli did not elicit the K-Complex but N350 still occurred. In both cases, the N350 was maximum at the vertex and declined in amplitude over anterior, posterior, and lateral sites. Harsh (1994) hypothesized that the N350 reflects a gradual inhibitory process of stimulus-related activation because it marks the cessation of behavioral responding to target stimuli during the sleep onset period.

In summary, the MMN mechanism for the detection of large stimulus changes seems to be at least partially automatic. An active neuronal representation of the standard stimuli is a prerequisite for detection of change. Fast rates of presentation do appear to maintain the memory representation for the standard even in sleeping subjects. The MMN is, however, attenuated for large deviance and is difficult to observe for small deviance. This is probably due to prior thalamic gating of stimulus input.

Table 4.1.

Large deviance: Mean amplitudes (μV) and standard deviations (parenthesis) of the difference waveforms at Fz for each 50 ms interval of the total 400 ms sweep

	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400
Alert Wake	0.53	-0.15	-2.94*	-1.10*	1.13	0.17	-1.34*	-1.43*
	(0.66)	(1.10)	(1.66)	(0.90)	(0.81)	(0.69)	(1.08)	(1.11)
Relax Wake	0.20	0.04	-1.98*	-0.86*	0.83	0.20	-1.00*	-0.96*
	(0.57)	(0.62)	(0.95)	(0.83)	(0.88)	(0.58)	(0.66)	(0.75)
Stage 1	-0.03	-0.34	-1.85*	-0.70	1.14	0.28	-1.68*	-1.16*
	(0.82)	(1.28)	(1.53)	(1.42)	(1.08)	(0.82)	(1.48)	(1.71)
Stage 2	-0.49	-0.86*	-1.79*	-1.09*	0.22	0.19	-1.62*	-1.87*
	(0.49)	(0.69)	(1.08)	(1.23)	(0.98)	(0.69)	(1.14)	(1.30)
SWS	-1.15*	-1.69	-2.34*	-1.90*	-0.94*	-0.41	-2.00*	-2.28*
	(1.67)	(3.03)	(3.23)	(2.31)	(1.15)	(1.69)	(2.81)	(3.38)

For all conditions n=12. except for SWS where n=11.
*Negative amplitude values significantly different from the baseline ($p<.05$).

Table 4.2.

Small deviance: Mean amplitudes (μV) and standard deviations (parenthesis) of the difference waveforms at Fz for each 50 ms interval of the total 400 ms sweep

	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400
Alert Wake	0.11	0.16	-0.61*	-0.86*	-0.27	0.30	0.08	-0.56*
	(0.28)	(0.46)	(0.95)	(0.77)	(0.56)	(0.49)	(0.56)	(0.82)
Relax Wake	0.14	0.42	-0.17	-0.12	-0.01	0.10	0.29	0.11
	(0.53)	(0.77)	(0.97)	(0.58)	(0.54)	(0.49)	(0.62)	(0.99)
Stage 1	0.21	0.42	0.15	-0.25	0.08	0.39	0.25	0.12
	(0.56)	(0.58)	(0.64)	(0.48)	(0.23)	(0.44)	(0.55)	(0.64)
Stage 2	-0.11	-0.12	0.02	-0.15	-0.27	-0.04	0.04	-0.11
	(0.34)	(0.41)	(0.34)	(0.27)	(0.30)	(0.29)	(0.40)	(0.34)
SWS	-1.27	-1.43*	-1.35*	-1.28	-0.70*	-0.85*	-1.60*	-1.18
	(2.40)	(2.05)	(1.57)	(2.48)	(1.18)	(0.94)	(2.32)	(2.57)

For all conditions n=12, except for SWS where n=11.
*Negative amplitude values significantly different from the baseline ($p<.05$).

Figure Captions

Figure 4.1. Grand-averaged waveforms following the standard (1000 Hz) and large deviant (2000 Hz) stimuli at all electrode sites in the different sleeping and waking conditions using the 0.16 Hz low analogue filter. The data were smoothed using a high-20 Hz digital filter.

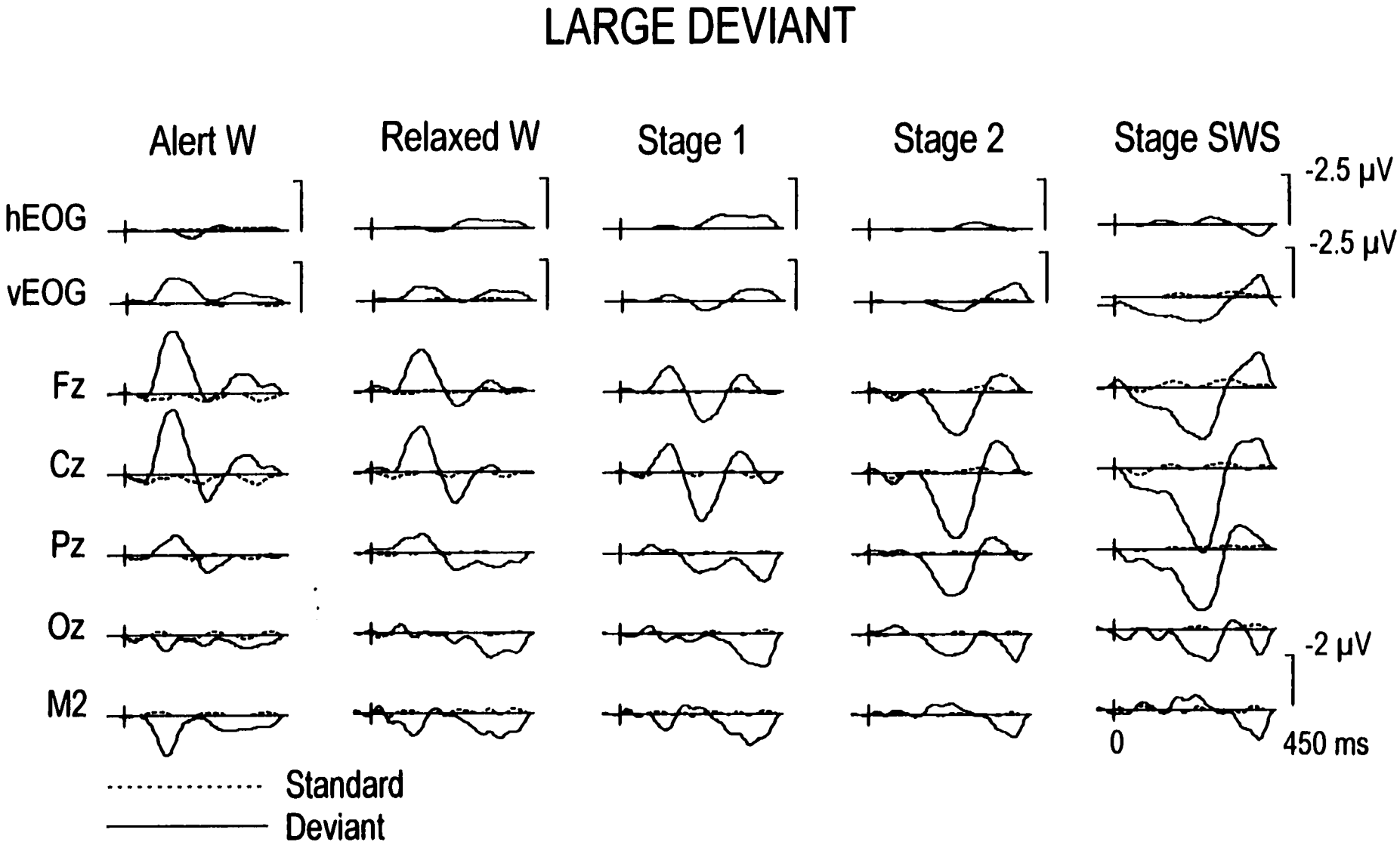
Figure 4.2. Grand-averaged waveforms following the standard (1000 Hz) and large deviant (2000 Hz) stimuli at all electrode sites in the different sleeping and waking conditions following the application of the low digital filter. Digital low and high filters were set at 3 and 20 Hz (3 dB attenuation), respectively.

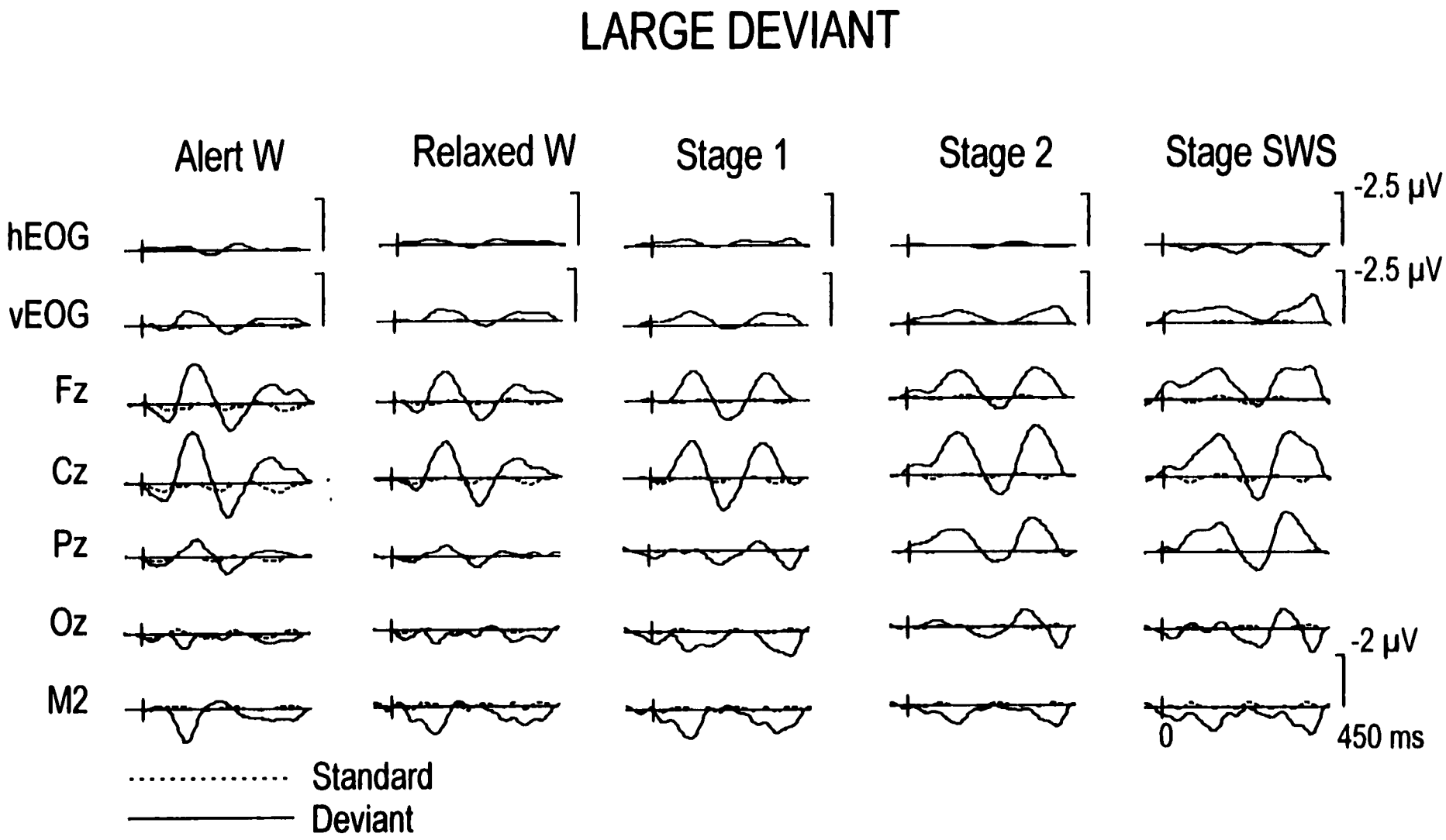
Figure 4.3. Grand-averaged large deviant difference waves at all electrode sites following the application of the low-3 Hz and high-20 Hz digital filters. The difference waves were computed by subtracting the standard from the large deviant waveforms observed in Figure 4.2.

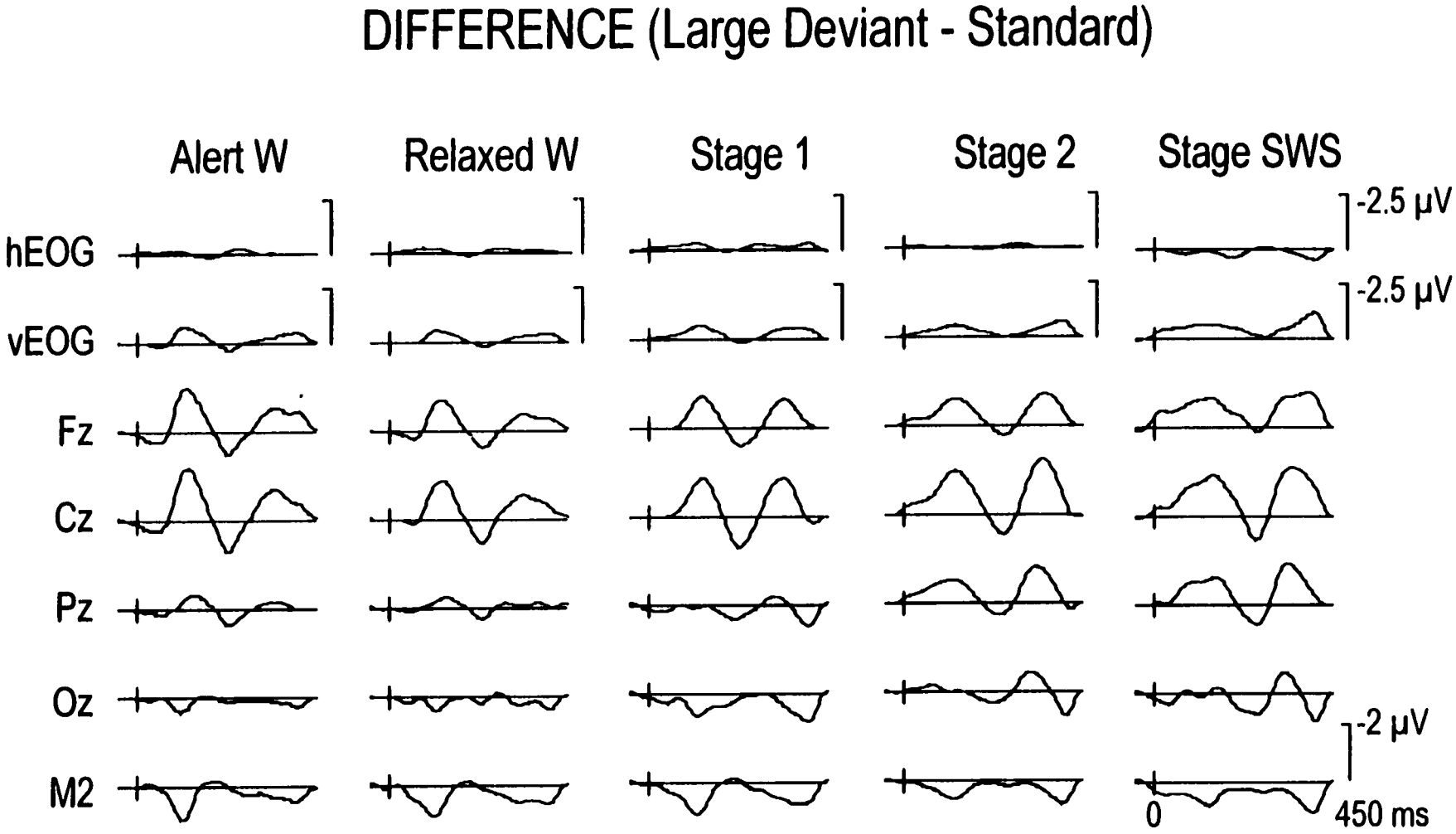
Figure 4.4. Grand-averaged waveforms following the standard (1000 Hz) and small deviant (1100 Hz) stimuli at all electrode sites in the different sleeping and waking conditions using the 0.16 Hz low analogue filter. The data were smoothed using a high-20 Hz digital filter.

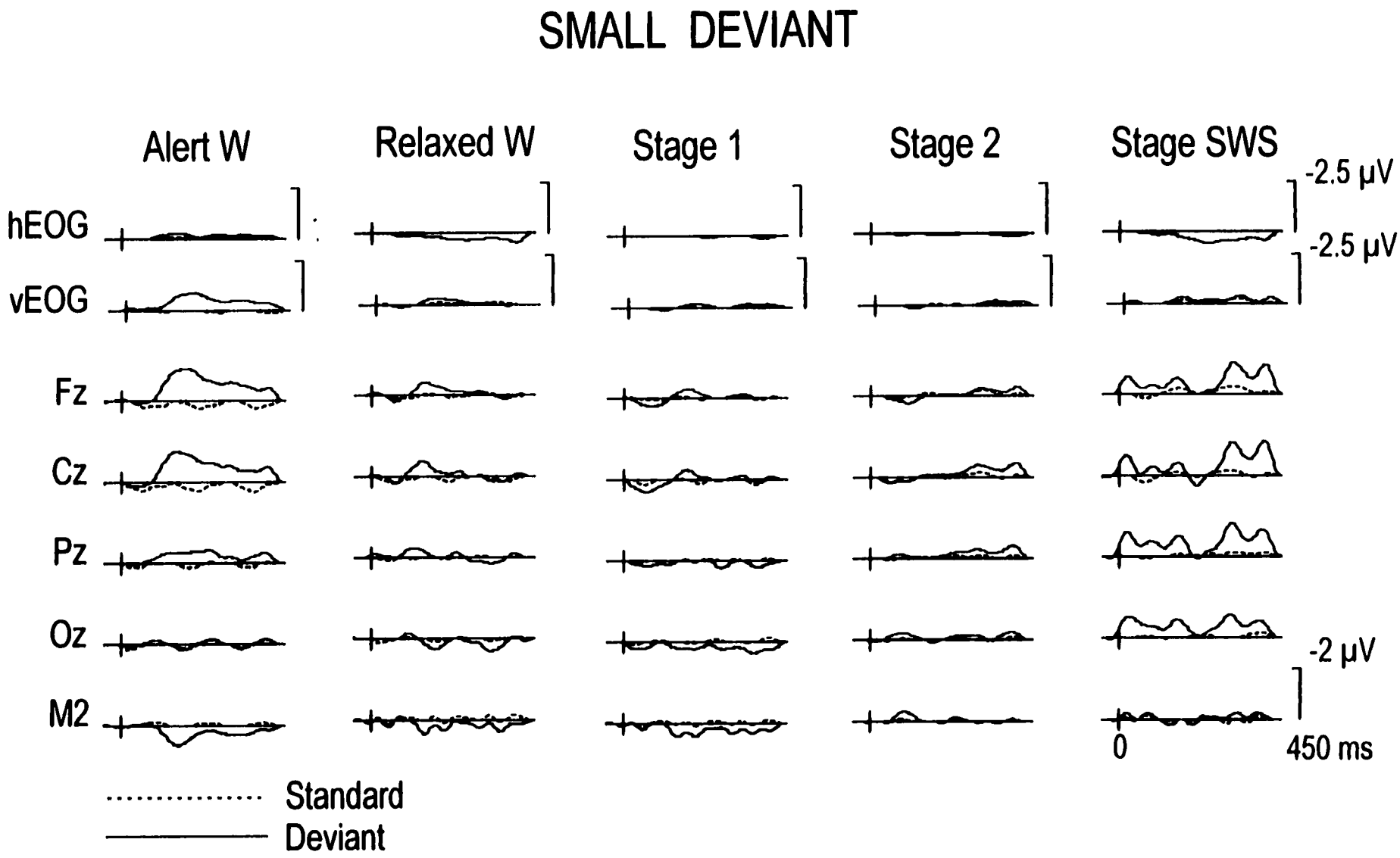
Figure 4.5. Grand-averaged waveforms following the standard (1000 Hz) and small deviant (1100 Hz) stimuli at all electrode sites in the different sleeping and waking conditions following the application of the low digital filter. Digital low and high filters were set at 3 and 20 Hz (3 dB attenuation), respectively.

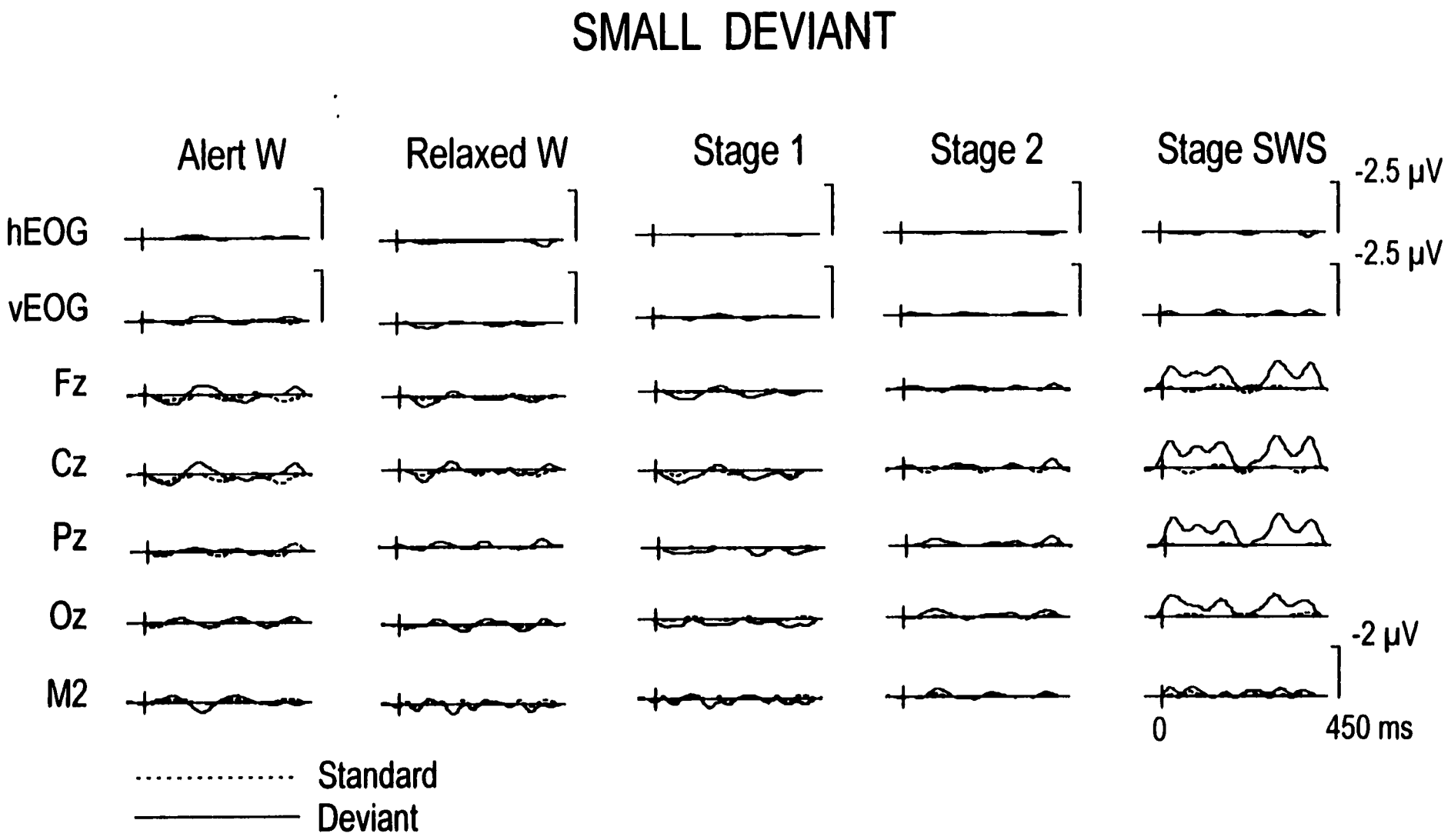
Figure 4.6. Grand-averaged small deviant difference waves at all electrode sites following the application of the low-3 Hz and high-20 Hz digital filters. The difference waves were computed by subtracting the standard from the large deviant waveforms observed in Figure 4.5.

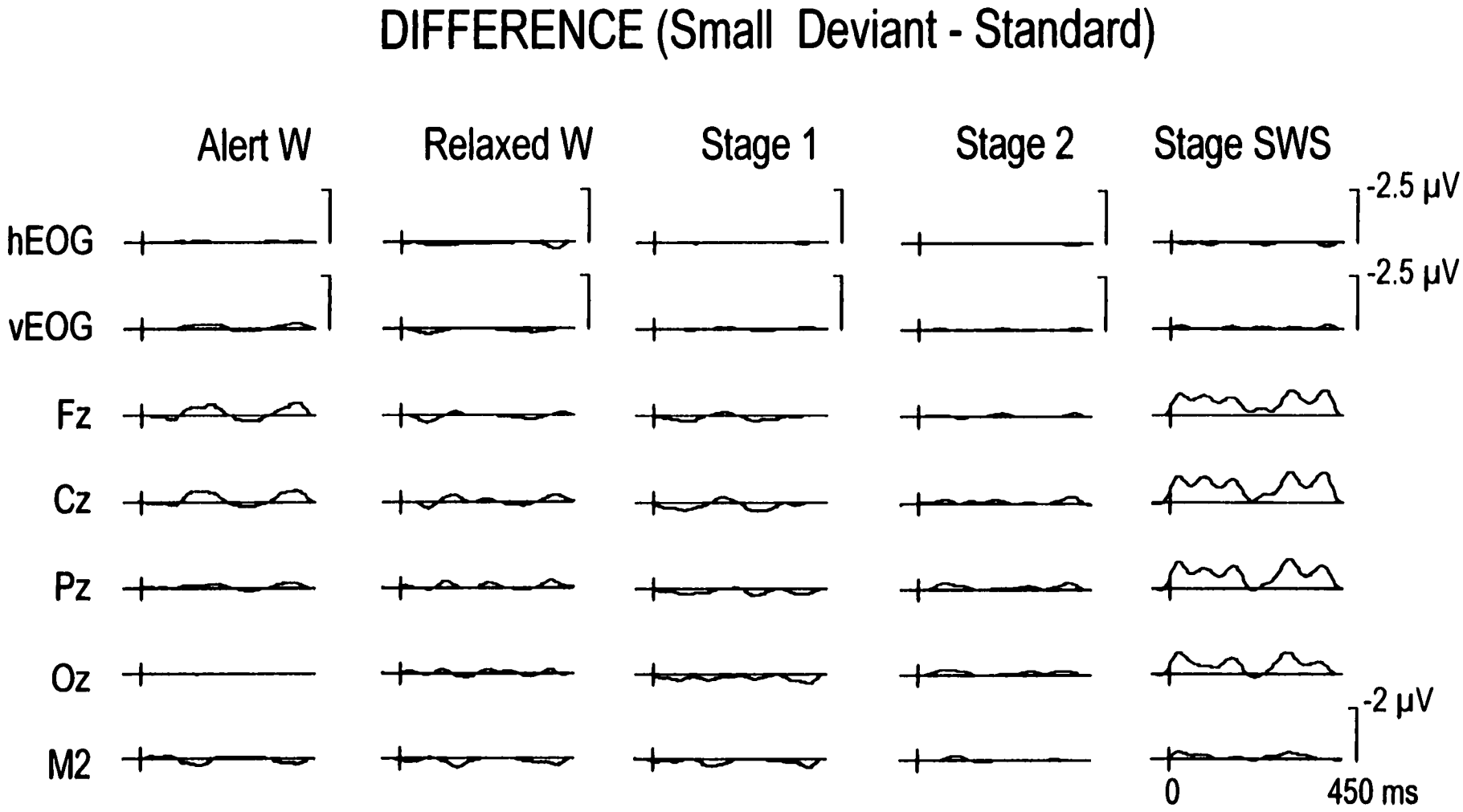

LARGE DEVIANT
Alert W
Relaxed W
Stage 1
Stage 2
Stage SWS
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-2.5 µV
-2.5 µV
-2 µV
0
450 ms
Standard
Deviant


LARGE DEVIANT
Alert W
Relaxed W
Stage 1
Stage 2
Stage SWS
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-2.5 µV
-2.5 µV
-2 µV
0
450 ms
Standard
Deviant


DIFFERENCE (Large Deviant - Standard)
Alert W
Relaxed W
Stage 1
Stage 2
Stage SWS
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-2.5 µV
-2.5 µV
-2 µV
0
450 ms


SMALL DEVIANT
Alert W
Relaxed W
Stage 1
Stage 2
Stage SWS
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-2.5 µV
-2.5 µV
-2 µV
0
450 ms
Standard
Deviant


SMALL DEVIANT
Alert W
Relaxed W
Stage 1
Stage 2
Stage SWS
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-2.5 µV
-2.5 µV
-2 µV
0
450 ms
Standard
Deviant


DIFFERENCE (Small Deviant - Standard)
Alert W
Relaxed W
Stage 1
Stage 2
Stage SWS
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-2.5 µV
-2.5 µV
-2 µV
0
450 ms

Chapter 5

General Discussion and Conclusions

To what extent is stimulus change detection independent of attention and conscious awareness? This dissertation investigated the effects of loss of consciousness on a cortical evoked response to stimulus change, the mismatch negativity (MMN). The MMN is elicited by an infrequent change or deviance in a train of otherwise repetitive, homogenous standard stimuli. The MMN is thought by many to be relatively independent of subjects' level of attention. Nevertheless, several studies employing intensity deviance found the MMN to be susceptible to attentional manipulation. However, when frequency deviants have been used, attention affects MMN amplitude only to small stimulus changes. Still, these results are difficult to interpret. In studies involving selective attention, a subject is generally asked to attend to one channel and ignore another. It is extremely difficult to design a study to determine the extent to which subjects actually were able to ignore the stimuli. In the waking state, it may be impossible for subjects to completely ignore stimuli. Sleep provides a crucial means to test the effects of loss of consciousness/attention on the MMN.

Three experiments investigated the role of sleep in the detection of change as reflected in the MMN. The purpose of Experiments 1 and 3 was to examine the presumed automaticity of MMN during the transition from wakefulness to sleep, the sleep onset period. Experiment 2 served as a technical investigation of the effects of probability and rate of stimulus presentation on MMN amplitude.

Summary of Findings

In Experiment 1, a long-lasting MMN was elicited during alert wakefulness (reading a book) following both small (1100 Hz) and large (2000 Hz) deviations in auditory frequency from a standard (1000 Hz). The SOA was 600 ms and the temporal probability of deviant occurrence was, on average, every 6 s (every 10 trials on average). Consistent with a large number of studies, in the alert wakefulness condition the MMN following the large deviant was relatively larger in amplitude compared with that to the small deviant. During relaxed wakefulness (when the subject was asked to fall asleep), the MMN to this large deviant remained statistically significant. However, this MMN was short-lasting and did not differ from the MMN elicited in the alert wakefulness condition within that same time interval. No MMN was observed following the small deviant in this condition. During Stage 1, a small nonsignificant MMN-like wave was observed following both small and large deviants. During Stage 2, however, an MMN was elicited, but only to the large deviant. This result appeared to contradict earlier reports that MMN cannot be recorded in NREM sleep. However, other studies presented stimuli during nocturnal sleep whereas the present study focused on the 5-15 minutes of the sleep-onset period. The finding that the MMN-like wave recorded in Stage 1 was smaller relative to that in Stage 2 can be explained by the poor signal-to-noise ratio. The duration of Stage 1 is very short. As such, fewer trials were available for averaging compared with Stage 2 of sleep. Thus, it is possible that despite the repeated awakenings of the subjects a significant amount of background noise remained in the Stage 1 average. The fact that the MMN following the small frequency change could not be elicited during sleep onset and within NREM itself was a novel finding. The MMN to the large deviant was followed by a late central-maximum negative wave, peaking

on average at 350 ms, in alert wakefulness, and Stages 1 and 2. In agreement with other studies, there was no evidence for MMN following either deviant during SWS.

Two possible interpretations were offered for the failure to elicit the MMN:

1. Failure of stimulus encoding. Stimulus input is inhibited prior to entry into the cortical sensory memory comparison system, probably at the level of the thalamus.
2. Fading of sensory memory. Stimulus input does reach the cortical sensory memory system. However, it is possible that sensory memory fades very rapidly during sleep. In Experiment 1, the memory for the standard stimuli might have faded within the 600 ms period before the deviant was presented.

To test these hypotheses requires that stimuli be presented very rapidly. In wakefulness, the amplitude of the MMN becomes smaller as the stimuli are presented slowly. The electrical MMN can no longer be recorded if stimuli occur every 4 s or slower. It is possible that during NREM sleep, a fast rate of presentation (600 ms) acts like a slow rate (1200 ms) in wakefulness. Unfortunately, relatively little is known about the interactive effects of rapid rate of stimulus presentation and probability of deviant occurrence on the MMN.

Experiment 2 was designed to examine these effects. For purposes of this dissertation, the primary interest was the effects of rapid rate of presentation on the MMN because results from this study were implemented in the final experiment. Auditory stimuli were 1000 Hz standard and 1100 Hz deviant. The probability of occurrence of the deviant was manipulated while SOA was either 150, 600, or 2400 ms. In general, a long-lasting MMN was evident in all conditions except at the longest SOA (2400 ms). The MMN remained large even when the SOA was 150 ms and the temporal probability of deviant occurrence was on average, every 4.5 s (a deviant every 30 trials on average). For purposes of studying the effects of sleep on the MMN, it

can be concluded that a robust MMN can be elicited even when stimuli are presented very rapidly provided that deviants occur relatively infrequently. These rate and probability parameters were used to set the presentation regimen in the final experiment.

In Experiment 3, a long-lasting MMN was elicited during alert wakefulness (reading a book) following both small (1100 Hz) and large (2000 Hz) deviations in auditory frequency from a standard (1000 Hz). The SOA was 150 ms and the temporal probability of deviant occurrence was 4.5 s (a deviant every 30 trials on average). The MMN following the small deviant was again reduced in amplitude compared with that following the large deviant. During the relaxed wakefulness condition, Stage 1 and NREM sleep, a long-lasting MMN was observed following the large deviant. This MMN was attenuated relative to that in the alert wakefulness condition. No differences were found, however, among the MMNs elicited in relaxed wakefulness and Stages 1 and 2. A small amplitude MMN was evident in relaxed wakefulness and Stages 1 and 2 following the small deviant, however these negativities were not different from baseline level. The MMN following the large deviant was followed by a late central-maximum negative wave, peaking on average at 350 ms, in both waking and sleeping states. This negativity also was observed following the small deviant but only in the alert wakefulness condition. These results support the hypothesis that the MMN comparison system is at least partially automatic. It can be elicited during non-REM sleep, at least for very large frequency deviance. The MMN following a small deviant is, however, difficult to observe during Stage 1 sleep or even as early as relaxed wakefulness. It is possible that during sleep onset cortical encoding of both the standard and deviant is weakened because of prior thalamic inhibition of sensory input.

In summary, Experiment 3 reported an MMN following the large deviant in all sleeping and waking states compared with waking states and only Stage 2 in Experiment 1. In addition, a

MMN-like negative wave, although not significant, was identified following the small deviant in the waking states and NREM sleep in Experiment 3.

The Nature of Change Detection

Threshold versus Probability Models

Fechner (1860/1966) viewed the experience of environmental change as the crossing of a fixed inner threshold of difference between two perceptual entities. The physical values of this threshold corresponds to the jnd. Thurstone (1927) criticized Fechner's threshold account, claiming that empirically-derived jnds are easily manipulated by stimulus factors such as the relative probabilities of standards and deviants. As an alternative, Thurstone proposed that change detection is inherently probabilistic, with each presentation of a stimulus creating a random perceptual effect along a sensory continuum. Thurstone's account characterized change detection as a noisy or sloppy system, one that was more or less efficient depending on exogenous and endogenous conditions.

Sensory versus Decisional Processes

Signal detection theory was an effort to specify the separate exogenous and endogenous mechanisms of change detection. In the theory, each stimulus presentation elicits a random perceptual effect. Across presentations, any given stimulus forms a Gaussian distribution of perceptual effects. The more physically similar two stimuli are, the more overlap between their respective distributions along a sensory evidence axis. The exogenous mechanism of change detection in this theory is perceptual sensitivity, the mean separation between perceptual

distributions scaled by their standard deviations. Sensitivity is estimated behaviorally by the statistic d', which measures how well two stimuli can be discriminated. A large value of d' indicates good perceptual sensitivity: the two stimuli are easy to distinguish, which leads to a high hit rate and a low false alarm rate. A large d' implies that the stimulus distributions are relatively far apart along the evidence continuum and/or that the distributional variances are relatively small. A small value of d' indicates poor perceptual sensitivity: the two stimuli are difficult to distinguish, which leads to a lower hit rate and a higher false alarm rate. A small d' implies that the stimulus distributions are close together along the evidence continuum and/or that the distributional variances are large.

According to signal-detection theory, change detection is also determined by endogenous decision processes. The greater the overlap between perceptual distributions the more uncertainty an observer undergoes in attempting to classify a given perceptual effect. To deal with the uncertainty, the observer is theorized to erect a decision boundary along the evidence axis. All perceptual effects exceeding this criterial value are classified as one stimulus (e.g., deviant or signal), and all effects below this value are classified as the other stimulus (e.g., standard or noise). When the probability of occurrence of a deviant stimulus is high, observers tend to erect a liberal criterion (i.e., a negative value of c), which leads to many hits, but also many false alarms. When the probability of occurrence of a deviant stimulus is low, observers tend to erect a conservative criterion (i.e., a positive value of c), which leads to fewer hits, but also fewer false alarms. The value of c is statistically independent of d'. Thus, a given deviant will yield a constant d', whether it is presented frequently or infrequently.

One problem with paradigms designed to evaluate signal detection theory is that they rely invariably on the active participation of a highly attentive and cooperative observer. The oddball

paradigm used in studying the MMN response is, in most ways, comparable to behavioral paradigms that have been used in the context of signal detection theory. Importantly, however, the MMN can be recorded in inattentive and unresponsive subjects. In this sense, it is relatively unaffected by the subjects' criterion for responding.

MMN and Change Detection

Relation of MMN to Perceptual Sensitivity

In the oddball paradigm, the deviant stimulus is presented relatively infrequently. Its presentation elicits an MMN response. The MMN brain generators must compare an incoming stimulus with a neural representation of an existing stimulus. The amplitude of the MMN is related directly to the extent of physical difference between the standard and the deviant. This physiological measure of stimulus discriminability thus is very similar to the behavioral measure, d'. Within saturation limits, the magnitude of the MMN response varies in direct proportion to perceptual sensitivity, as measured by d'. Small physical differences between standard and deviant are more difficult for observers to discriminate -- and lead to a smaller amplitude MMN -- than do large physical differences between the stimuli. For example, in their study of auditory clicks embedded in background noise, Sabri and Campbell (2000; see Appendix A for manuscript) found that observers' accuracy improved as the intensity of the signal increased. Importantly, MMN amplitude covaried with performance accuracy. Results such as these suggest that MMN represents the bioelectric expression of perceptual sensitivity to change detection.

Neutralizing Response Bias

By recording ERP components to investigate change detection, overt behavioral responses can be avoided. This approach, which was adopted in the present dissertation, conferred several advantages. First, it permitted the study of change detection mechanisms during the removal of overt attention to stimuli, whether the observer was fully awake (reading a book), awake but relaxed (in bed), falling asleep (Stage 1), or fully asleep (NREM). Manipulations of attention removal are unworkable within a traditional behavioral paradigm. Indeed, those paradigms are restricted to investigations of change detection during conscious attention to stimulus differences.

Second, by eliminating classification responses from the detection paradigm, any response biases ostensibly were eliminated from the paradigm. In other words, because the observer was not required, and usually unable, to respond, no decision processes contributed to the ERP change response. In principle, then, the methodology used in this dissertation permitted a rare glimpse at perceptual sensitivity uncontaminated by decisional shifts or biases. If this conclusion is valid, then one implication is that the MMN effects observed in this study archly reflect the separation or variability of perceptual stimulus distributions along the sensory continuum, free of decision thresholds.

Relation of MMN to Decision Criterion

The foregoing conclusion and its implications can be challenged, however. Recall in Experiment 2 of this dissertation that MMN amplitude was affected strongly by the probability of deviant occurrence: As the temporal or sequential probability of the deviant increased, the amplitude of the MMN decreased (see also Näätänen, 1992; Näätänen et al., 1983). In signal-

detection theory, manipulations of the probability of deviant occurrence alter the decision criterion, but have no effect on perceptual sensitivity (i.e., for a given physical difference between standard and deviant). In fact, by causing systematic shifts in the hit and false alarm rates, stimulus probability manipulations create a single ROC curve (plot of false-alarm rates against hit rates) in discrimination space, the area of which serves as an alternative measure of perceptual sensitivity (Green & Swets, 1966). If similar probability manipulations yield systematic shifts in MMN amplitude, then one might argue that MMN also reflects decisional processes independent of perceptual sensitivity. This interpretation calls into doubt the claim that MMN is a "pure" measure of sensory change detection.

Independence of MMN and Decision Processes

A comparison between the results of Experiments 1 and 3 militates against viewing MMN as a decision-based component. Temporal probability of deviant occurrence was purposely decreased in Experiment 3 relative to Experiment 1 with the aim of enhancing MMN amplitude during NREM sleep. The fact that robust MMN responses were obtained during NREM sleep in Experiment 3 (relative to Experiment 1) confirms that probability manipulations are effective in elevating MMN magnitude during sleep, as Experiment 2 showed during wakefulness. Yet, because observers in Experiments 1 and 3 were tested while sleeping, and hence could make no conscious judgments about the stimuli or their probability of occurrence, one can hardly argue that the probability manipulation across these experiments affected their decision-making criteria. Of course, one might assert that an "unconscious response bias" contributed to MMN magnitude, the implication being that response bias extends beyond what is consciously decisional. But the term "unconscious response bias" is oxymoronic because in

ordinary jargon stimulus classification implies conscious response processing. On the basis of the present results, therefore, it is more parsimonious to conclude that the MMN elicited in a truly passive paradigm is unaffected by decisional processes.

Sensory and Memory Constituents of Change Detection

Role of Memory in Change Detection

What, then, is the nondecisional role of stimulus probability to change detection? In the Introduction to this dissertation, it was claimed that the detection of deviants in an oddball paradigm may depend on sensory memory for standard stimuli. In a signal-detection experiment, an ideal observer may optimize performance by relying on sensory memory, responding (to deviant/signal presence) on any trial during which a perceptual difference is noticed between the memory of the previous stimulus and the experience of the current stimulus. Disruption of sensory memory also could serve as the basis of change detection in the oddball paradigm, even when the observer's attention is directed away from the stimuli. Indeed, the MMN response is thought by many to be the automatic neural outcome of a comparison process between the deviant representation and sensory memory trace of the standard. To the extent that the strength of that memory trace covaries with the magnitude of the MMN response once a stimulus change occurs, one could claim that memory processes partly underlie change detection. Following this line of reasoning, to the extent that repeated presentations of the standard stimulus (i.e., low deviant probability) strengthens its corresponding memory representation, stimulus probability plays an intimate role in change detection.

The Durlach-Braida Model

Traditional signal-detection theory provides little room for nondecisional effects of memory on change detection. Sensitivity to stimulus change customarily has been reduced to the mean and variance of sensory distributions. In later years, however, psychophysicists incorporated memory processes into formal characterizations of change detection. The most influential of these modern signal-detection models was proposed by Durlach and Braida (1969). Their ideas emerged from an analysis of auditory intensity resolution in an absolute identification paradigm. Their research demonstrated that perceptual sensitivity varies not only with the magnitude of intensity difference between stimuli, but also with the rate of stimulus presentation and the size of the stimulus set (see also Siegel, 1972). On the basis of these results, Durlach and Braida hypothesized that intensity resolution depends jointly on a sensory process and a memory process.

Sensation variance is a function of physical difference between stimuli. With all other factors being equal, the more similar physically two stimuli are to each other, the more limited performance will be by the variance in their perceptual effects. Sensation variance thus corresponds closely to the notion of distributional overlap in traditional signal-detection theoretics.

Memory variance is a function of the sequential and temporal factors that establish short-term sensory memories. With all other factors being equal, the less often a stimulus is presented, and the larger the pool of stimuli from which it is drawn, the more limited performance will be by the variance in memory representation. Analogous to sensation variance, the more widely distributed the memory representation, the greater the overlap among stimuli (in memory), and thus the poorer the stimulus resolution. Conversely, the more frequently and exclusively a

stimulus is presented, the smaller its memory variance, and hence the easier it is to identify and distinguish it from other stimuli.

Extension of the Durlach-Braida Model to MMN

Although originally developed to explain behavioral performance in absolute identification paradigms, we can extend the Durlach-Braida model to account for the MMN effects obtained in the oddball paradigm used in the present study. Let us assume that the MMN component is a decision (or response bias) free measure of stimulus change. Let us assume further that the measure reflects two factors that mediate change detection: sensation variance and memory variance. Limitations on the MMN response could therefore be imposed by whichever source of variance is emphasized in a particular experimental setup. A design that specifies a small physical difference between standard and deviant puts a premium on sensation variance. The relatively small MMN magnitude generated in such a design primarily reflects limitations on change detection imposed by high sensory overlap. A design that specifies slow and infrequent presentation of the standard puts a premium on memory variance. The relatively small MMN magnitude generated in this design chiefly reflects limitations on change detection imposed by a weak memory trace of the standard stimulus.

This framework can be used fruitfully in interpreting the results of the present dissertation. In Experiment 2, for example, the design emphasized memory variance, keeping sensory variance constant. Accordingly, the strongest MMN response was produced by the presentation regimen that minimized memory variance: a rapid SOA, frequent presentation of the standard, and infrequent presentation of the deviant. Because the sensation variance was unchanged (identical stimuli across conditions), the differences observed across conditions must

be rooted in corresponding differences in memory variance. Experiments 1 and 3 manipulated sensation variance by including two different deviants, while keeping memory variance constant (i.e., a single presentation regimen was used within each experiment). One might reasonably suppose, then, that in these experiments sensation variance was relatively less for the large deviant, which was physically more dissimilar to the standard. Accordingly, the strongest MMN response was produced by the more dissimilar deviant.

The comparative results of Experiments 1 and 3 can now be examined in a new light. Between the experiments, the sensation variance was held constant (identical stimuli), but the memory variance was not. In particular, Experiment 3 capitalized on the results of Experiment 2, using an increased presentation rate (Experiment 3: 150 ms; Experiment 1: 600 ms) and a decreased probability of deviant occurrence (Experiment 3: every 30 trials; Experiment 1: every 10 trials) to minimize memory variance in the standard. Consequently, MMN responses consistently were more robust in Experiment 3 than in Experiment 1, in keeping with the overall reduction in memory variance. Note that this explanation rejects any role to nonconscious decision processes (see the section *Independence of MMN and Decision Processes*).

Attention and Change Detection

Effects of Sleep on Sensation Variance

What are the effects on change detection of removing attention through sleep? Sleep could conceivably degrade either the sensory information or memory information (or both) available for the processing of environmental change. Sleep is associated with an enhanced gating of sensory information by thalamic nuclei to higher cortical mechanisms (Steriade et al., 1993). Campbell et al. (1992) reported that the auditory P1, N1, and P2 components exhibit

significantly greater positivity during NREM stages of sleep (i.e., Stage 2 and slow-wave sleep) than during the waking state (see also Nielsen-Bohlman, Knight, Woods, & Woodward, 1991). They conjectured that the sleep-induced positivity might reflect the thalamic suppression of information processing during sleep, with inhibitory processes operating within 25 ms of stimulus onset (see also Sabri et al., 2000). The implication is that inhibitory sleep mechanisms accentuate stimulus sensation variance.

Increased sensation variance in sleep may be the byproduct of thalamic sensory gating. Psychophysical research by Luce, Green, and Weber (1976) indicates that attentional precuing to a critical band of the auditory frequency spectrum enhances perceptual sensitivity. On their account, attention acts to decrease the variability in perceptual effects, thereby elevating d'. The converse may characterize the effects of sleep. The removal of attention to stimuli that accompany sleep may blur the precision of perceptual activation along the sensation scale, boosting sensation variance, and hence undermining change detection. The results of the present study fit with this account. In particular, in Experiments 1 and 3 NREM sleep led to the massive reduction of an MMN response to the small deviant and to the reduction in MMN amplitude to the large deviant. The increased overlap between perceptual distributions induced by the removal of attention during sleep may well be the source of decreased sensitivity to both the small and large deviant within these experiments.

Effects of Sleep on Memory Variance

From the available evidence, it is unclear whether sleep also alters the memory variance of standard stimuli. During NREM sleep, cerebral blood flow is globally reduced as compared with both waking and REM sleep states (Braun, Balkin, Wesensten, Gwadry, Carson, Varga,

Baldwin, Belenky, & Herscovitch, 1998; Maquet, Péters, Aerts, Delfiore, Degueldre, Luxen, & Franck, 1996). Neural activity is depressed in many regions including the prefrontal cortex, thalamus, the reticular activating system, and basal ganglia. However, sensory areas, such as the auditory cortex, where the MMN generator is located, appear to remain active (Maquet, Degueldre, Delfiore, Aerts, Péters, Luxen, & Franck, 1997). Thus, NREM sleep may degrade input to the MMN generators but appears to have little direct effect on the actual activity of the generators. Of course, as argued earlier, an enhanced MMN response in Experiment 3 compared with Experiment 1 could be traced to the beneficial effects of presentation rate on memory variance. Nonetheless, compared with the waking state, the MMN response was reduced during NREM in both Experiments 1 and 3, whether or not rate parameters were optimized. Thus, it is conceivable that sleep has no direct effect on sensory memory mechanisms, but that a reduction in memory variance partially can offset the detrimental effects of sleep on sensation variance. Further research will be needed to explore this issue more thoroughly.

Is Change Detection Automatic?

Näätanen (1990, 1992) argued that MMN reflects an automatic discrimination of auditory stimulus change, using traces left by previous auditory stimulation. In the present dissertation, the case has been made that change detection -- as reflected in the MMN response -- is comprised of separate sensory and memory constituents. Using waking versus sleeping states as an attention manipulation, it has been shown that MMN amplitude is not completely independent of attention, but neither is it abolished by the withdrawal of attention, at least when presentation parameters are optimized. The effects of sleep on the MMN are consistent with those observed in attention studies in which subjects ignore the stimuli and perform a primary task (Alain &

Woods, 1997; Näätanen, 1991; Näätanen et al., 1993; Trejo et al., 1995; Woldorff et al., 1991). In those studies, however, the extent to which awake and alert subjects ignore the stimuli cannot be tested and quantified. Sleep offers a unique tool for controlling the attention directed towards changing stimuli.

The fact that the withdrawal of attention reduces the magnitude of MMN indicates that change detection is not fully automatic. Indeed, this thesis has argued that sleep may undermine the sensation variance intrinsic to change detection. Nevertheless, the fact that remnants of the MMN response remain even in the deepest stages of sleep -- when conscious attention is maximally withdrawn -- suggest strongly that change detection is, at the least, a partially automatic process. It is doubtful that the partial automaticity of change detection is a point midway along a continuum of automaticity (cf. Cohen et al., 1990; Logan, 1985; MacLeod & Dunbar, 1988; but see Logan, 1988). Rather, partial automaticity reflects the fact that at least some of the constituents of the change detection process -- either sensation variance or, more probably, memory variance -- are immune to the most severe retractions of conscious attention. It is of no small biological or evolutionary significance that change detection mechanisms operate in even these most unaroused states.

Conclusions

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

1. Changes in the amplitude of the frequency MMN following both small and large deviants begin as early as the relaxed wakefulness state (subjects attempt to fall asleep) when the MMN is markedly attenuated.

2. The MMN, although reduced in amplitude, can be elicited in Stages 1 and 2 of sleep at least for large frequency deviants.
3. The small frequency deviance did not elicit MMN during definitive sleep, but not even during the sleep onset period.
4. If loss of consciousness is marked by the absence of the MMN, then SWS is probably the transition point for large deviance. This transition can begin early as relaxed wakefulness for small deviance.
5. In wakefulness, the MMN to frequency deviants can be elicited even when stimuli are presented very rapidly provided that deviants occur relatively infrequently (every 2 s or longer).
6. A MMN following the large deviant is apparent in SWS when rate of stimulus presentation is rapid. However, insufficient number of trials and poor signal (small amplitude MMN)-to-noise (high amplitude background EEG) ratio caused a "noisy" waveform thus preventing conclusive results.
7. Large and small frequency deviants elicit late negativities peaking at 350 ms after stimulus onset in alert wakefulness. These might represent a subsequent MMN to the standard stimulus or alternatively, a marker of sleepiness.
8. Large frequency deviants elicit late negativities in NREM sleep that conform to the latency and scalp distribution of sleep-induced N350.
9. Sensory encoding of the standard stimulus appears to be disrupted during Stages 1 and 2 of sleep as observed by the changes in N1. The amplitude of N1, a measure of general consciousness, and P2 following the large deviant stimulus is markedly affected by sleep onset and sleep. The deviant N1 gradually decreases in amplitude from alert wakefulness

to Stage 2 of sleep. During SWS, it is below baseline. Similarly, the amplitude of P2 gradually increases in amplitude from alert wakefulness to SWS.

10. The MMN memory comparison system operates during sleep onset and NREM sleep provided that cortical sensory encoding is adequate. This may only be the case for large stimulus change.

11. The MMN component appears to be at least partially (but not totally) automatic.

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Appendix A

Mismatch Negativity to Inclusions and Omissions of Stimulus Features

Abstract

Two experiments were run to determine the effects of addition or removal of a stimulus feature on the Mismatch Negativity (MMN). In the first experiment, a deviant stimulus was constructed by adding a click to a white noise standard stimulus. In the second experiment, the deviant was constructed by subtracting the click from the standard. In different conditions, the intensity of the click was varied. When the deviant was constructed by the addition of a click, a significant MMN was evident in those conditions in which click-to-noise ratio exceeded 1.0. When the deviant was constructed by the subtraction of the click, a significant negativity was found only when the click-to-noise ratio was very large. However, this negativity was accompanied by only a small polarity inversion at the mastoid. The MMN is thus best elicited when the deviant stimulus contains a new afferent element not present in the standard stimulus.

Introduction

The mismatch negativity (MMN) is an event-related potential component (ERP) that is elicited as a response to an infrequent "deviant" auditory stimulus occurring within a train of repetitive "standards".[1] The MMN is seen as a negative deflection, maximum over fronto-central sites, typically peaking between 150 and 250 ms after deviant onset. The MMN can be elicited for any discriminable change in a sound sequence. It has been elicited by deviants that vary in tonal frequency,[1, 2] intensity,[3] duration,[4] spatial location,[5] interstimulus interval,[6, 7] or phonetic properties.[8, 9, 10] In most MMN studies, standard and deviant stimuli are usually spectrally simple pure tones. Complex acoustic stimuli, such as noise, phonemes, or mixtures of pure tones have at times also been employed and will elicit the MMN.[10-14]

Nordby et al. investigated the effects of inclusion or omission of a complex sound on MMN elicitation. The authors found that the magnitude of MMN differed depending on whether the deviant involved the inclusion or the omission of stimulus elements. The MMN was larger when the deviant was constructed by the addition of an acoustic feature to the standard, and was significantly reduced when the deviant was constructed by the removal of an acoustic feature from the standard. It is possible that the removal of stimulus features is more difficult to perceive than their addition. The MMN is much reduced in amplitude when the perceptual contrast between standard and deviant cannot be detected easily.[10, 13-15] Unfortunately, Nordby et al. did not provide behavioral detection rates in their various conditions.

In the present study, stimuli were again constructed by the addition or removal of an acoustic feature. The extent of perceptual contrast between the standard and the deviant was manipulated in four different conditions. Behavioral indices of deviant detection were also

incorporated. Two experiments were run. In the first experiment, the deviant was constructed by adding a square wave click to a noise burst standard. In the second experiment, the deviant was the noise burst while the standard was constructed by adding a click to this noise. Thus, in the first experiment the deviant was constructed by the *inclusion* of a click while in the second, it was constructed by the *omission* of the click. The intensity of the click was varied across conditions in both experiments.

Materials and Methods

Experiment 1

Subjects. Ten healthy university students (aged 20-30 years) were paid an honorarium for their participation in the study. Subjects signed a consent form following an explanation of the nature of the experiment. This study was conducted following the ethical guidelines of the Medical Research Council of Canada.

Procedure and Stimuli. Subjects were seated in a sound-attenuated chamber and instructed to read a self-selected book, thus ignoring the auditory stimuli. Stimuli were presented binaurally through headphones. The standard stimulus was 65 dB SPL white noise burst of 100 ms duration with a rise-and-fall time of 50 ms. The deviant stimulus was constructed by adding (mixing) a biphasic (condensation-rarefaction) 2 ms duration square wave "click" to the white noise. The click began 49 ms after onset of the noise. The intensity of the click stimulus was either, 62, 65, 68, or 71 dB peak equivalent SPL in different conditions. The noise and click+noise deviant stimuli are illustrated in Figure 1. The noise standard was presented on 85% of trials and the click+noise deviant on the remaining 15% of trials. The order of presentation of

the different stimuli was randomized with the restriction that a minimum of three standard stimuli separated each deviant stimulus. The constant stimulus onset asynchrony (SOA) was 512 ms. A total of 600 trials were presented in each condition. Conditions were presented in a random order. Each condition was repeated two times in order to assure replicability of results. The ability of the subjects to discriminate the deviant was determined in separate conditions, following the recording of the MMN. Click intensities of 65 and 68 dB were employed in two different conditions. Participants were asked to press the space bar on a computer keyboard upon detection of the deviant stimulus.

-----Insert Figure 1 about here-----

EEG recording. EEG activity was recorded from four channels using tin cup electrodes placed on Fz, Cz, Pz, and the right mastoid. The nose served as a reference. A vertical EOG was recorded from electrodes placed at the supra- and infra-orbital ridges of the right eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. The ground electrode was placed on the forehead. Inter-electrode impedances were below 2kΩ. Data were acquired continuously using a 256 Hz sampling rate. The high filter was set at 30 Hz. The time constant was 2 s. EOG artifact was corrected using an algorithm operating in the frequency domain. The EEG signals were later reconstructed into discrete epochs beginning 50 ms prior to stimulus onset and continuing for 450 ms following it (i.e., a total sweep time of 500 ms). ERPs were subsequently digitally low-pass filtered using an inverse FFT algorithm with a 20-Hz high frequency cutoff.

Data measurement and statistical analysis. Difference waveforms were computed by subtracting, point-by-point, the standard from the deviant waveforms at each electrode site within a condition. The 450-ms post-stimulus period was subdivided into nine 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. The average of all data points in the 50 ms pre-stimulus period served as a baseline from which all interval amplitudes were measured. Confidence intervals were then computed for each of the 9 latency intervals in order to evaluate whether the mean amplitudes for each interval significantly differed from zero baseline. This procedure is equivalent to computing a *t*-test between the standard and deviant waveforms.[16] To restrict the likelihood of a chance finding, the time window of occurrence and the scalp topography were constrained to conform to that observed in literature. MMN had to occur only within a 100-350 ms time window after stimulus onset and be larger frontally/centrally than parietally. In addition, a polarity inversion had to be observed at the mastoid (M2). A one-way analysis of variance (ANOVA) was performed to determine significant difference between conditions and time intervals containing the MMN. All differences were considered to be significant at $p < .05$.

Experiment 2

Ten healthy university students (aged 20-30 years) also participated in the study. None of these subjects had participated in the first experiment. The standard ($p = .85$) was a click embedded in white noise and the deviant ($p = .15$) stimulus was the white noise burst. Thus, the deviant was constructed by the removal of the click from the standard stimulus. Again, four different click intensities were employed in different conditions. EEG recording, data measurement and statistical analysis were identical to those used in Experiment 1.

Results

The grand average ERP difference waveforms for each condition in both Experiments appear in Figure 2 and 3. The mean Fz amplitudes of the difference waveforms for each 50-ms interval appear in Table 1 and 2 for Experiments 1 and 2, respectively.

Experiment 1. When the deviant was constructed by the inclusion of a stimulus feature (click+noise), the hit rate was .96 and .60 in the 68 and 65 dB conditions, respectively. Mean reaction times were 464 ms and 598 ms, respectively.

A significant MMN was evident only in those conditions in which click-to-noise ratio exceeded 1.0 (i.e., 68 dB and 71 dB). The deviant-standard difference at Fz and Cz was significant in both the 151-200 and 201-250 ms intervals (i.e., 100-200 ms after click onset) for these intensities. The mastoid (M2) showed a polarity reversal in both intervals. The MMN in the 68 dB condition was significantly smaller in amplitude and longer in duration than in the 71 dB condition. When the click intensity was lowered to 65 dB, a small negative-going wave was observed in the 201-250 ms interval. This negativity, however, was not significantly different from baseline. No MMN was visible when the click intensity was lowered to 62 dB.

-----Insert Figure 2 and Tables 1 about here-----

Experiment 2. When the deviant was constructed by the omission of a stimulus feature (noise alone), behavioral performance was poorer than Experiment 1. Hit rates were .67 and .39 in the 68 and 65 dB conditions, respectively. Mean reaction times were 548 ms and 650 ms, respectively. A significant long-lasting negativity was found only when the click-to-noise ratio was largest (i.e., when the intensity of the click was 71 dB). However, this negativity was

accompanied by only a small inversion in polarity at the mastoid (M2). No significant negativities were observed at any time interval for any of the lower intensity stimuli.

-----Insert Figure 3 and Table 2 about here-----

Discussion

Perception of deviance is poorer when stimulus elements have been omitted from a standard than when they have been added to it. Subjects in Experiment 2 (omission) had significantly lower hit rates and longer RTs when the click was removed from the target than subjects performing the same conditions in Experiment 1 (inclusion) when the click was added to the target, regardless the intensity of the click. These results suggest that change detection is asymmetrical. Perceptual systems appear to be better at discriminating between two stimuli when the environmental change involves inclusion than when it involves exclusion. Nonetheless, it is important to emphasize that subjects in both experiments performed significantly better than at chance level when detecting deviants. Thus, compared with stimulus inclusion, stimulus omission decreases, but does not eliminate, stimulus discriminability.

The observed behavioral asymmetry was accompanied by an asymmetry in the MMN, which was evident clearly only when change involved inclusion. When the click-to-noise ratio was greater than 1.0, a significant MMN was observed. Its amplitude was larger and occurred earlier when the intensity of the click was 71 compared to 68 dB. When the intensities of the click and noise were equivalent (i.e., 65 dB), only small and nonsignificant amplitude MMN was discernable. The behavioral hit rate in this condition dropped to .65. Thus, as subjects' detection

performance becomes increasingly poorer, the MMN becomes progressively reduced in amplitude.

When the deviant was constructed by the removal of the click from the click+noise standard, the behavioral hit rate was .67. In this condition, a significant negativity was observed only for the loudest click accompanied by a very small polarity inversion at the mastoid. It is thus questionable whether the fronto-central negative wave can be considered a true MMN. A similar negativity was not observed when lower intensity clicks were employed as the standard stimulus. By contrast, the negativity found in the inclusion conditions was larger for different intensities, returned to baseline sooner and showed a larger inversion in polarity at the mastoid.

Nordby et al. also found evidence of a MMN to a noise burst deviant characterized by the removal of a pure tone. Again, this MMN was much attenuated compared to that observed in the inclusion condition of the same element. One interpretation of these results is that the MMN response is mainly sensitive to new afferent elements in a stimulus array. Alternatively, it is possible that the negative deflection in response to inclusion is in fact a summation of both the N1 and MMN components. N1 amplitude increases following the addition of a new acoustic feature, such as, an increase in tone's intensity.[17] Also, N1 typically peaks sharply at 80-100 ms after stimulus onset and like the MMN, has a fronto-central scalp distribution. However in our case, when a loud click was added, a long-lasting negativity was observed from 100 to 250 ms following click onset. This is more characteristic of the MMN than of N1.

The use of white noise as a deviant in this and the Nordby et al. study may represent a special case of stimulus feature omission. It may be, for example, that distinct neural mechanisms underlie change detection of simple compared to complex acoustic stimuli. Cortical detection of simple acoustic stimuli such as pure tones takes place in the primary auditory cortex.

On the other hand, cortical detection of more spectrally complex stimuli such as noise and speech sounds occurs widely in the supratemporal planes of the auditory cortex.[18-20] Noise can also be detected earlier, in the auditory brainstem nuclei.[21, 22] Perceptual discriminability of spectrally simple and complex deviants might thus be accomplished differently. To distinguish this hypothesis from the idea of new-afferent elements, it will be important to design tests that omit elements from noise-free composite stimuli, such as complex tonal stimuli.

Conclusion

Our results demonstrate that manipulation of click-to-noise ratio is consistent in maintaining the pattern revealed in other studies for omission of stimulus elements when noise served as the deviant (Nordby et al., 1994).[12] When click added to noise served as the deviant, the magnitude of MMN varied with the intensity of the click stimulus. However, when noise alone served as the deviant and the click+noise as the standard, no such relationship appeared. A possible MMN was observed only when the deviant and standard stimuli were markedly different. These results can be explained in terms of new afferent elements as a distinct MMN is best elicited when the deviant contains additional features that are not part of the standard stimuli. Alternatively, it is possible that using white noise as the deviant stimulus in studying omission of stimulus elements might be viewed as a special case in which detection of the deviant will not necessarily be associated with a MMN.

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Table 1

Click+noise deviant: mean amplitudes (μV) and standard deviations (parenthesis) of the difference waveforms at Fz for each 50 ms interval of the total 450 ms sweep

	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
Click Intensity									
62 dB	0.17	0.65	0.60	0.37	0.32	0.07	0.01	0.48	0.76
	(0.83)	(0.96)	(1.22)	(1.08)	(1.40)	(1.65)	(1.71)	(1.82)	(1.56)
65 dB	0.41	0.53	0.54	0.05	-0.66	-0.27	0.27	0.36	0.14
	(1.31)	(1.37)	(1.61)	(1.74)	(1.78)	(1.71)	(1.80)	(1.85)	(1.62)
68 dB	-0.05	-0.10	-0.54	-1.06*	-1.06*	-0.81	-0.28	-0.66	-0.88
	(1.01)	(1.14)	(1.74)	(1.68)	(1.81)	(2.05)	(2.38)	(2.63)	(2.59)
71 dB	-0.07	-0.28	-0.92	-1.34*	-1.00*	-0.23	-0.20	0.25	-0.26
	(0.72)	(0.82)	(1.64)	(1.50)	(1.36)	(0.96)	(1.33)	(1.55)	(2.03)

For all conditions n=10. except for click intensity 62 dB where n=9.

* $p < .05$

Table 2

Noise deviant: mean amplitudes (μV) and standard deviations (parenthesis) of the difference waveforms at Fz for each 50 ms interval of the total 450 ms sweep

	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450
Click Intensity									
62 dB	0.33	0.14	0.07	0.25	0.40	0.00	0.15	0.13	-0.07
	(0.82)	(1.38)	(1.49)	(1.17)	(0.87)	(0.93)	(1.07)	(1.20)	(1.37)
65 dB	-0.30	-0.33	-0.15	-0.16	-0.46	-0.31	-0.69	-1.28	-1.48
	90.91)	(0.91)	(1.03)	(1.68)	(1.75)	(1.13)	(1.20)	(1.32)	(1.55)
68 dB	0.06	-0.01	-0.19	-0.14	0.10	0.32	0.63	0.39	0.27
	(0.49)	(0.89)	(0.93)	(0.83)	(0.86)	(1.07)	(0.99)	(1.01)	(1.32)
71 dB	-0.41	-0.28	-0.30	-1.14*	-0.92	-1.05	-1.33*	-1.24*	-1.29*
	(1.36)	(1.00)	(1.40)	(1.56)	(1.86)	(2.20)	(1.81)	(1.35)	(1.47)

For all conditions n=10.

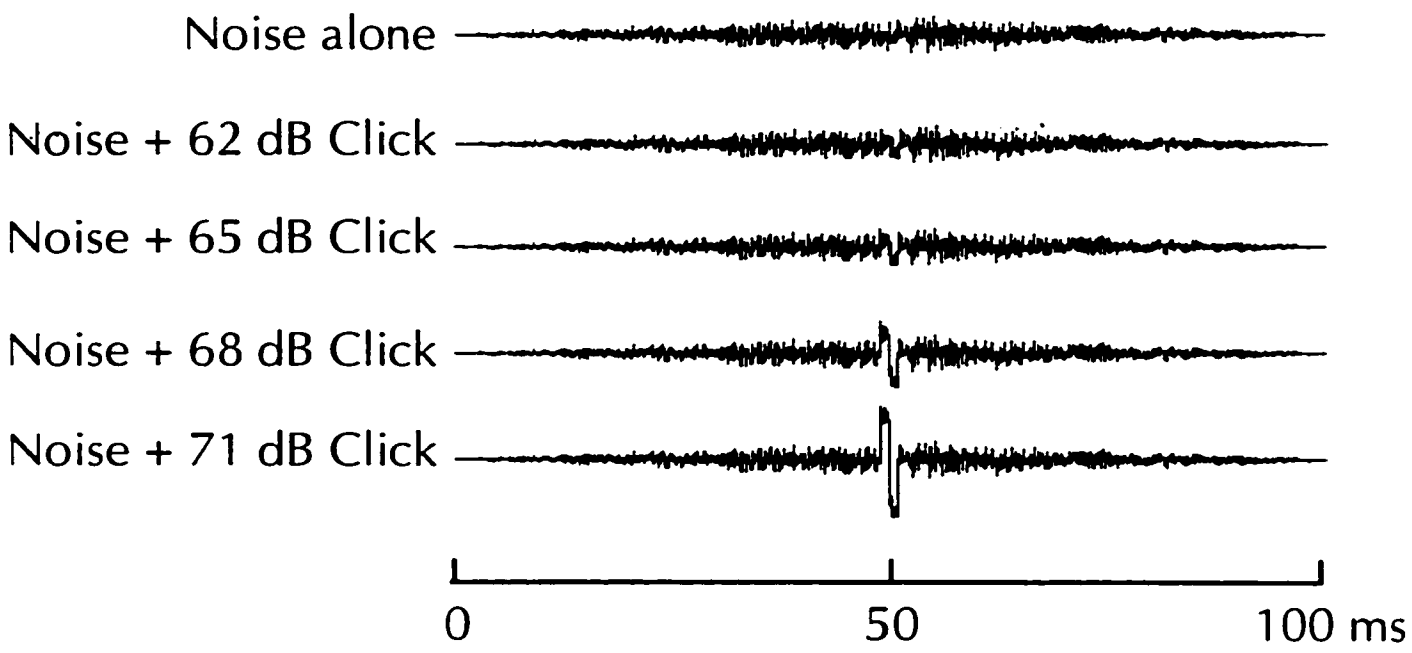
* $p < .05$

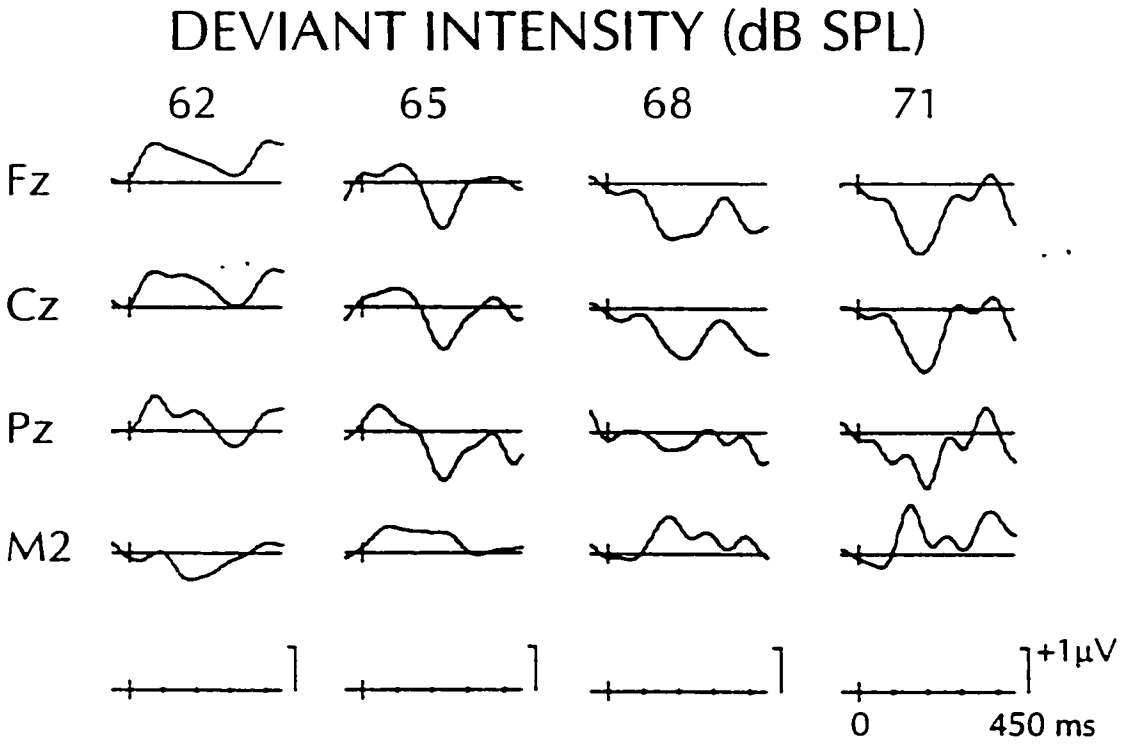
Figure Captions

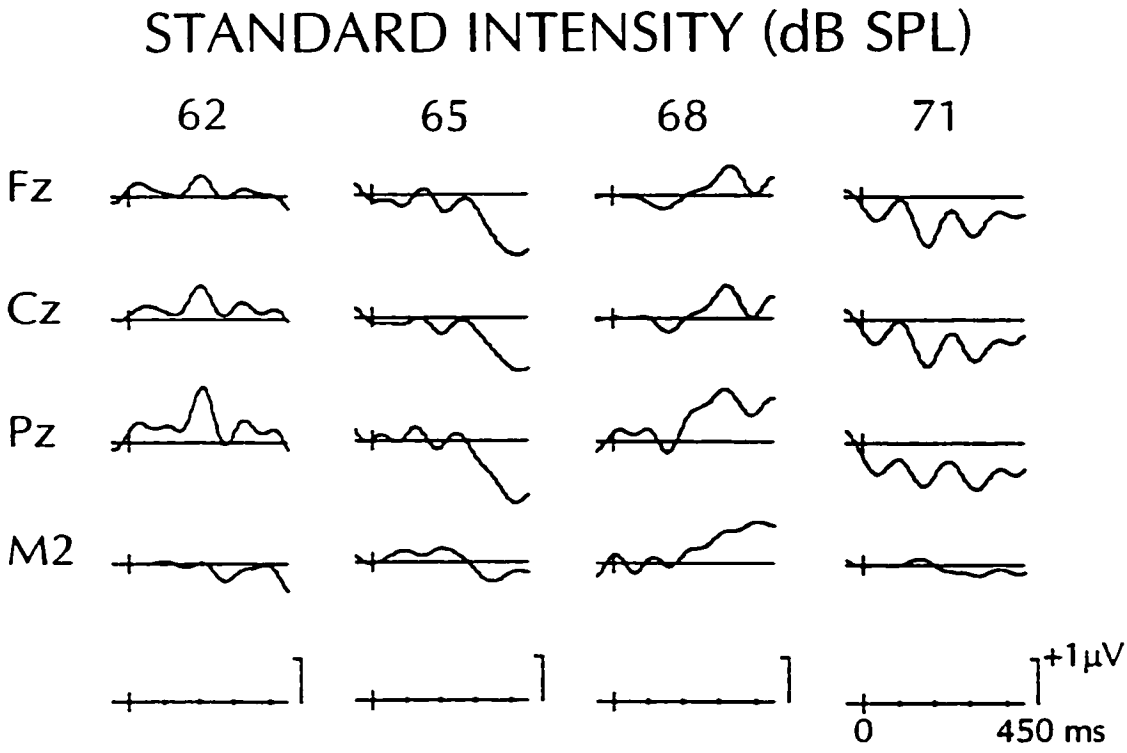
Figure 1. The different types of stimuli employed in Experiment 1 and 2. In Experiment 1, white noise alone was used as the standard stimulus. The deviant was constructed by adding a biphasic 2 ms duration square wave click to this noise. In different conditions, the click's intensity was 62, 65, 68, or 71 dB SPL. In experiment 2, white noise alone served as the deviant. In different conditions, noise+click stimuli served as the standard.

Figure 2. Grand average difference waveforms for 62, 65, 68, or 71 dB click intensities, using Click+Noise as the deviant stimuli. Negativity is plotted downward.

Figure 3. Grand average difference waveforms for 62, 65, 68, or 71 dB click intensities, using White noise as the deviant stimuli. Negativity is plotted downward.


Noise alone
Noise + 62 dB Click
Noise + 65 dB Click
Noise + 68 dB Click
Noise + 71 dB Click
0
50
100 ms


DEVIANT INTENSITY (dB SPL)
62
65
68
71
Fz
Cz
Pz
M2
+1μV
0
450 ms


STANDARD INTENSITY (dB SPL)
62
65
68
71
Fz
Cz
Pz
M2
+1μV
0
450 ms