INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

Université d'Ottawa • University of Ottawa

Event-Related Potentials and Behavioural Responses Associated with a Loss of Consciousness at Sleep Onset

by

© Duncan R. de Lugt

Thesis Document submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

School of Psychology, University of Ottawa
Ottawa, Ontario, Canada

May 1997

ABSTRACT

This thesis examined changes in the brain's responses ("evoked potentials") during the transition from consciousness to unconsciousness. A negative wave, "N1", peaking at about 100 ms is affected by the subject's extent of attention/consciousness. Unfortunately, this same peak is also affected by manipulation of the physical parameters of the stimulus. The extent to which a component is affected by a physical or psychological parameter is often difficult to determine in the awake and alert subject. There are two principal reasons for this. Manipulation of the physical stimulus may inadvertently cause a change in the psychological state of the subject. Thus, subjects will attend to louder stimuli even if not asked to do so. Manipulation of the subject's level of attention also poses a dilemma. The change in the level of attention is always relative, not absolute. When subjects are asked to ignore stimuli, they are not able to do so. The sleep period provides a convenient means to resolve this dilemma. It is the period of time during which subjects are least attentive to, and thus least conscious of, their external environment. It can therefore be used to provide a baseline - near absolute level of attentiveness.

Three experiments were run. In the first experiment, tones were presented to subjects at a rapid 600 ms interstimulus interval, during sleep onset (the transition period from Wakefulness through to Stage 2 of sleep). Subjects were not

required to respond to the stimuli. A late negative wave, "N1", peaking at about 100 ms, was attenuated to near baseline level in Stage 1 of sleep while earlier and later positive waves, P1 and P2, were augmented. Thus, sleep onset was associated with the removal of an overlapping negative slow wave, the wNd wave, from the P1-N1-P2 complex. The removal of this long-lasting negative slow wave appeared earlier in the sleep onset period than had been reported in previous studies. This early change in the brain's responsiveness to external stimuli was perhaps due to the monotony associated with the rapid rate of stimulus presentation. This may have prevented the periodic arousals that can occur when stimuli are presented at slower rates. Alternately, the early changes may have been the result of subjects not having to overtly respond to the eliciting stimuli.

In Experiment 2 stimuli were presented at a relatively slow rate (every 1000 ms). Again, subjects were not required to make an overt response. The removal of the wNd wave from the P1-N1-P2 complex was again noted but this effect did not take place until Stage 2 of sleep. Thus, stimuli presented relatively slowly may "intrude" into consciousness thereby delaying definitive sleep.

In Experiment 3 spatial resolution was enhanced by recording from 29 scalp electrode sites. Topographic changes to the P1-N1-P2 evoked potential complex during sleep onset were investigated. In addition, several novel methodological changes were implemented in this final study. Stimuli were presented in an oddball paradigm. Rare "target" tones were randomly presented

within a train of frequently occurring standard stimuli. Subjects were required to press a hand held button whenever they detected a target stimulus. Target detections were rare in Stage 2 of sleep and were made on about half of target presentations in Stage 1. The wNd wave was partially removed from the P1-N1-P2 complex during Stage 1 of sleep and was fully removed at Stage 2, reducing N1 to baseline level. A late positive P3 response was also observed in response to the rare, target stimuli. P3 was largest to the detected targets in Wakefulness and Stage 1 of sleep, and was significantly decreased in amplitude to the missed targets in Stage 1, disappearing to near baseline levels during Stage 2 of sleep. The decrease in subject's P3 response was parallelled by the decrease observed in the amplitude of the N1 and subjects' reduced behavioural response to the target stimuli. The scalp topographies of the N1b (the vertex component of the N1 complex) and wNd waves were very similar. Both were maximum over fronto-central areas of the scalp. In addition, current source density maps of the N1b and wNd waves also showed similar topographies. Because of the similarity of the N1b and wNd spline and current source density maps, there is no evidence that the intra-cranial generators of these waves are different.

As the subject gradually loses consciousness, the amplitude of the slow negative wave, wNd, that begins at about 30 ms following the stimulus and lasting for about 250 ms, gradually decays in amplitude. It reaches baseline level during definitive sleep. A radical interpretation of the present data is that a

late negative wave, "N1", is entirely endogenous in nature. N1 may reflect the extent of the subject's conscious awareness of the external stimulus. As such, the N1 component of the auditory evoked potential provides a convenient and easy means to monitor the level of attention/consciousness in a number of applied settings.

ACKNOWLEDGEMENTS

I would be remiss if I did not take this opportunity to thank those who have helped me throughout my academic career. First, I would like to thank Dr. Robert Stelmack, my co-advisor and colleague. Bob, I have always appreciated your advice and opinions which have influenced me more than you realize. I would also like to thank Dr. Joseph de Koninck in whose research lab some of this data was collected. It was recently said (at a Friday wine & cheese) that Joseph was a "good-being", something which I believe is evident to anyone he meets. Thanks also to Dr. Verner Knott, my M.Sc. thesis advisor, without whose help and encouragement I may not have pursued my Ph.D.

I am also grateful to Dr. Ian Bell, whose InstEP program was instrumental for the collection of this data. Thanks also to Herman van den Bergen, Bob Spratt and Martin Gillet for their technical assistance. If things in the lab went wrong, they were quickly fixed (or if something unusual was needed, then it was invented) ... the amplifiers really worked well!

My time at the University was also made very rewarding by the stimulating and thoroughly enjoyable "Friday meetings" spent with staff and students alike. These meetings were often both cathartic and intellectually stimulating. One original Friday regular and co-investigator in some of this research, Derek Loewy, has been missed since he left for his post-doc. Derek, school just hasn't been quite the same. Thanks also to Kim Côté,

another co-investigator, colleague and Friday regular.

Throughout my studies, I have always been encouraged and supported by my parents, parents-in-law, and especially by my wife Nicola. It goes without saying that the pursuit of a Ph.D. can at time be very stressful, both for the candidate and for those close to him. Nicola, you have shown great patience and understanding during my time at school. It's success is due, in no small part, to your support. Thank you.

Finally, I would like to express my sincere thanks and appreciation to my advisor and friend, Dr. Kenneth Campbell. Without your help and guidance this thesis would never have been completed. During the time I have spent at the University of Ottawa I have learned a great deal, academically and otherwise, and have had many good times. I was fortunate to have had you as my advisor for my doctoral studies.

Thanks Ken.

CURRICULUM STUDORIUM

Duncan de Lugt was born in Ndola, Zambia on the 18th day of February, 1965. He completed his Bachelor of Arts (Honours) degree in Psychology at Carleton University in 1987. He continued his studies part-time, completing his Master of Science degree in Psychology with a specialization in Neuroscience at Carleton University in 1992. During his studies, he published a series of articles and abstracts, and presented papers at various scientific meetings, symposia and conferences.

CONTRIBUTIONS TO RESEARCH

CHAPTERS

Campbell, K.B. and de Lugt, D. Event-related potential measures of cognitive deficits following closed head injury. In: F. Boller and J. Grafman (Eds.), Handbook of Neuropsychology, Volume 10. Amsterdam: Elsevier Science Publishers, 1995: 269-297.

JOURNAL ARTICLES

de Lugt, D., Loewy, D., and Campbell, K. The effect of sleep onset on event-related potentials with rapid rates of stimulus presentation. Electroencephalography and Clinical Neurophysiology, 1996, 98: 484-492.

Knott, V. and de Lugt, D. Subjective and brain evoked responses to electrical pain stimulation: Effects of cigarette smoking and warning condition. Pharmacology, Biochemistry and Behaviour, 1991, 39: 889-893.

Knott, V., Lapierre, Y., de Lugt, D., Griffiths, L., Bakish, D., Browne, M. and Horn, E. Prepatory brain potentials in major depressive disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 1991, 15(2): 257-262.

Knott, V., Lapierre, Y., Griffiths, L., de Lugt, D. and Bakish, D. Event-related potentials and selective attention in major depressive illness. Journal of Affective Disorders, 1991, 23: 43-48.

PUBLISHED ABSTRACTS

Bonato, R., Marquardt, C., Orr, L., Loewy, D., de Lugt, D. and Radonjic, D. A comparison of the Magellan Monitor and polysomnography in the assessment of daytime sleepiness: A preliminary investigation. In: M.H. Chase, L.D. Rosenthal, C. O'Connor (Eds.), Sleep Research 1996, 25, Brain Information Service/Brain Research Institute, UCLA, Los Angeles, 1996: 482.

Côté, K., de Lugt, D. and Campbell, K. Topographical analysis of the auditory evoked K-complex. In: M.H. Chase, L.D. Rosenthal, C. O'Connor (Eds.), Sleep Research 1996, 25, Brain Information Service/Brain Research Institute, UCLA, Los Angeles, 1996: 5.

Côté, K.A., Perrino, A., de Lugt, D. & Campbell, K.B. Changes in event-related potentials during the transition from wakefulness to sleep. Psychophysiology, 1996: 33, (suppl. 1), p. 31.

de Lugt, D. and Campbell, K. Long latency evoked potentials as measures of auditory thresholds during sleep. Psychophysiology, 1995: 32, (suppl. 1), p. 27.

de Lugt, D., Côté, K. and Campbell, K. Topographical analysis of the N100 auditory event-related potential at sleep onset. Journal of Sleep Research, 1996: 5 (suppl. 1), p. 46.

de Lugt, D., Loewy, D. and Campbell, K. The effects of the rate of stimulus presentation on auditory evoked potentials at sleep onset. In: M.H. Chase, T. Roth and C. O'Connor (Eds.), Sleep Research, Volume 24A. Brain Information Service/Brain Research Institute, UCLA, Los Angeles, 1995: 20.

de Lugt, D., Côté, K., Lee, W. & Campbell, K. Topographic analysis of the N100 auditory event-related potential during the transition to sleep. Psychophysiology, 1996: 33, (suppl. 1), p.34.

de Lugt, D., Loewy, D., Jeakins, D., Bonato, R. and Radonjic, D. Period amplitude analysis of EEG: Pre- and post-periodic leg movements in stage 2 sleep. In: M.H. Chase, T. Roth and C. O'Connor (Eds.), Sleep Research, Volume 24A. Brain Information Service/Brain Research Institute, UCLA, Los Angeles, 1995: 294.

de Lugt, D. and Knott, V. N400, language processing, and negative symptomatology in schizophrenia. Psychophysiology, 1995: 32, (suppl. 1), 27.

Loewy, D., de Lugt, D. and Campbell, K. The effect of sleep onset on event-related potentials to stimulus deviance. Journal of Sleep Research, 1994: 3 (suppl. 1), 147.

Loewy, D., de Lugt, D., Bonato, R., Jeakins, D. and Radonjic, D. An investigation of sleep-state misperception in chronic insomnia. In: M.H. Chase, T. Roth and C. O'Connor (Eds.), Sleep Research, Volume 24A. Brain Information Service/Brain Research Institute, UCLA, Los Angeles, 1995: 341.

Loewy, D., de Lugt, D., Campbell, K., Elton, M. and Kok, A. Detection of deviation in auditory intensity persists in REM sleep. In: M.H. Chase, T. Roth and C. O'Connor (Eds.), Sleep Research, Volume 24A. Brain Information Service/Brain Research Institute, UCLA, Los Angeles, 1995: 40.

POSTER PRESENTATIONS & CONFERENCE PROCEEDINGS

Bonato, R., Marquardt, C., Orr, L., Loewy, D., de Lugt, D. and Radonjic, D. A comparison of the Magellan Monitor and polysomnography in the assessment of daytime sleepiness: A preliminary investigation. Poster presented at: Association of Professional Sleep Societies, June, 1996, Washington, D.C., U.S.A.

Côté, K., Perrino, A., de Lugt, D. and Campbell, K. Changes in event-related potentials during the transition from wakefulness to sleep. Poster presented at: The Thirty-Sixth Annual Meeting of the Society for Psychophysiological Research, October 1996, Vancouver, British Columbia, Canada.

Côté, K., de Lugt, D. and Campbell, K. Topographical analysis of the auditory evoked K-complex. Poster presented at: Association of Professional Sleep Societies, June, 1996, Washington, D.C., U.S.A.

de Lugt, D. and Campbell, K. Long latency evoked potentials as measures of auditory threshold during sleep. Poster presented at: The Thirty-fifth Annual Meeting of the Society for Psychophysiological Research, October 1995, Toronto, Ontario, Canada.

de Lugt, D., Côté, K. and Campbell, K. Topographical analysis of the N100 auditory event-related potential at sleep onset. Poster presented at: The 13th Congress of the European Sleep Research Society, June 1996, Brussels, Belgium.

de Lugt, D., Côté, K., Lee, W. and Campbell, K. Topographical analysis of the N100 auditory event-related potential during the transition to sleep. Poster presented at: The Thirty-Sixth Annual Meeting of the Society for Psychophysiological Research, October 1996, Vancouver, British Columbia, Canada.

de Lugt, D., Loewy, D. and Campbell, K. The effects of the rate of stimulus presentation on auditory evoked potentials at sleep onset. Poster presented at: The World Federation of Sleep Research Societies Second International Congress, September 1995, Nassau, The Bahamas.

de Lugt, D., Loewy, D., Jeakins, D., Bonato, R. and Radonjic, D. Period amplitude analysis of EEG: Pre- and post-periodic leg movements in stage 2 sleep. Poster presented at: The World Federation of Sleep Research Societies Second International Congress, September 1995, Nassau, The Bahamas.

de Lugt, D. and Knott, V. N400, language processing and negative symptomatology in schizophrenia. Poster presented at: The Thirty-fifth Annual Meeting of the Society for Psychophysiological Research, October 1995, Toronto, Ontario, Canada.

Knott, V. and de Lugt, D. Subjective and brain evoked responses to electrical pain stimulation: Effects of cigarette smoking and warning condition. Poster presented at: The Fourth International Evoked Potential Symposium, October 1990, Toronto, Ontario, Canada.

Knott, V., Lapierre, Y., de Lugt, D., Griffiths, L., Bakish, D., Browne, M. and Horn, E. EEG frequency correlates of psychomotor retardation in depression. Poster presented at: The University of Ottawa/McGill University - Research Day, November 1991, Montreal, Quebec, Canada.

Knott, V., Lapierre, Y., Griffiths, L., de Lugt, D. and Bakish, D. Event-related potentials and selective attention in major depressive illness. Poster presented at: The Fourth International Evoked Potential Symposium, October 1990, Toronto, Ontario, Canada.

Loewy, D., Campbell, K., Bastien, C., de Lugt, D. and Bonato, R. Event-related potential measures of stimulus deviance detection in sleep. Poster presented at: Association of Professional Sleep Societies, June, 1994, Boston, Massachusetts, U.S.A.

Loewy, D., Campbell, K., de Lugt, D. and Bonato, R. Changes in the auditory N1 at sleep onset. Poster presented at: Association of Professional Sleep Societies, June 1994, Boston, Massachusetts, U.S.A.

Loewy, D., de Lugt, D. and Campbell, K. The effect of sleep onset on event-related potentials to stimulus deviance. Poster presented at: Eurosleep '94 12th Congress of the European Sleep Research Society, May 1994, Florence, Italy.

Loewy, D., de Lugt, D., Bonato, R., Jeakins, D. and Radonjic, D. An investigation of sleep-state misperception in chronic insomnia. Poster presented at: The World Federation of Sleep Research Societies Second International Congress, September 1995, Nassau, The Bahamas.

Loewy, D., de Lugt, D., Campbell, K., Elton, M. and Kok, A. Detection of deviation in auditory intensity persists in REM sleep. Poster presented at: The World Federation of Sleep Research Societies Second International Congress, September 1995, Nassau, The Bahamas.

TABLE OF CONTENTS

Chapter

ABBREVIATIONS USED THROUGHOUT THIS DOCUMENT

A/D	analogue-to-digital
ANOVA	analysis of variance
AW	alert wakefulness
BAEP	brainstem auditory evoked potential
CSD	current source density
dB	decibel
EEG	electroencephalogram
EMG	electromyogram
EOG	electro-oculogram
EP	evoked potential
ERP	event-related potential
Hz	Hertz (cycles per second)
ISI	interstimulus interval
kOhms	kilo-Ohms
ms	millisecond
MMN	mismatch negativity
Nd	negative difference
NREM	non-REM sleep
PN	processing negativity
REM	rapid eye movement
RFM	the mid-point between RM and Fz
RM	right mastoid
RT	reaction time
RW	relaxed wakefulness
S1	Stage 1 sleep
S2	Stage 2 sleep
s	second
SD	standard deviation
S/N	signal-to-noise ratio
SO	sleep onset
SP	spline potential
SPL	sound pressure level
SWS	slow wave sleep
μV	microvolt
W	Wakefulness
wNd	waking negative difference

ORGANIZATIONAL NOTE

This dissertation consists of five chapters. Chapter 1 presents a review of the literature and develops the rationale for the three experiments which follow. Chapters 2, 3 and 4 present the results from these experiments. They are presented in journal article format. Each chapter, therefore, includes separate Introduction, Method, Results and Discussion sections. Each study is preceded by a single page which provides a brief rationale for that experiment. D. de Lugt is (or will be) the senior author on all three publications. Chapter 2 was published in the journal Electroencephalography and Clinical Neurophysiology (1996, 98: 484-492). Chapter 3 has been submitted to the International Journal of Psychophysiology, and Chapter 4 is in preparation for submission to Electroencephalography and Clinical Neurophysiology. There may be some overlap in the Introductions of these articles, however, the remaining sections should contain minimal overlap as the methods, results and discussions are different for each experiment. The fifth and final chapter provides a general discussion which integrates the three experiments. A summary of the novel findings and claims is also provided. A complete Reference list is presented at the end of the thesis, rather than at the end of each chapter, to avoid redundancy.

Chapter 1

REVIEW OF THE LITERATURE

Consciousness

A common theme during 19th century philosophy and psychology was the study of consciousness. It dominated the writings of the founder of experimental psychology, Wundt, and the founder of psychoanalysis, Freud. These psychologists investigated consciousness using introspection and self observation. Their techniques, however, proved to be unreliable, mainly because of the subjective nature of their measurement. James (1890), later described the mechanisms of conscious awareness and attention although his writings are based more on philosophical speculation than on empirical data.

The study of consciousness was severely criticised by the American behaviourist movement led by Watson (1913). Consciousness is a private mental experience. Thus, contrary to science's objective-materialist doctrine, consciousness cannot be directly observed, although it might be indirectly inferred. Moreover, an operational definition of "consciousness" has proven to be exceedingly difficult. The behaviourists, therefore, claimed that a phenomenon that could not be easily defined, observed nor measured was deemed to be unworthy of the scientific study of psychology. It was not until the cognitive revival following World War II that a more flexible cognitive approach

based on an information processing/cybernetic model was adopted.

Initially, the cognitive approach began in England, far from the shores of American behaviourism. Broadbent (1958) in Cambridge, and Treisman (1964) in Oxford, developed models for the selective attention process. These form the basis of many of the models that are still used today. At any given moment, vast amounts of physical stimulation in our environment continuously bombard our senses. The role of attention is to allow only the most relevant of information to reach conscious awareness. In order for relevant information to attain consciousness, the processing of the irrelevant must be inhibited or "gated". The information processing system is assumed to have a limited capacity. The system must therefore "choose" which types of information will be processed. Failure to do so will result in an overloading of our limited capacity to process information.

A long series of studies in experimental cognitive psychology has examined the nature of the attentional process. Many different questions have been asked (e.g. Where is the location of the "gate" or filter? How many are there? What types of information can be filtered? How do different stimulus parameters - intensity, rate of presentation, etc. - affect the efficacy of the attention system). Answers to many of these questions remain unresolved due, in part, to the limitations of measurement in experimental psychology. Most experimental psychologists employ performance or "behavioural" measures such as the subject's accuracy of performance and/or the speed of

their reaction time. They then infer back to the hypothetical stages of information processing that were affected by their experimental manipulations. Real-time brain processing cannot be observed directly but can only be inferred as a consequence of behaviour. Today's behaviourists continue to emphasize that reliance on inferential methods rather than on direct observation is scientifically untenable. In spite of the cognitive "revolution" in the 1970's and 1980's, the behaviourist, B.F. Skinner, remained vehemently opposed to the study of such inferred but overtly unobservable mental events (see for example, Skinner 1975).

In the study of attention, the experimental psychologist relying on strict performance measures encounters another methodological barrier. A major concern in this field is for the fate of the unattended channel. To what extent is information in the unattended channel processed? This question is not easily answered. The researcher can employ performance measures or subjective self-report as evidence that the subject was attending to a particular task. Thus, an overt response can be used as evidence that the subject made a conscious detection. However, what evidence would suffice to conclude that the subject was *not* attending? It is difficult to design an experiment in which the subject makes an overt response to a stimulus that they are asked to ignore. The very fact that a subject is asked to detect an unattended stimulus will obviously direct attention to this stimulus. The unattended then becomes attended! On the other

hand, the interpretation of a failure to respond to ignored stimuli is also ambiguous. Either the subject could ignore the stimulus and thus was not consciously aware of it or they, in fact, were consciously aware of it (because of intrusions into consciousness) but followed instructions and did not respond. Philosophically, it is illogical to conclude a subject is not doing something (not attending) on the basis of a failure to respond.

A number of cognitive psychophysiologists record the brain's electrical activity (EEG) during different attentional states. This method has the advantage that brain activity during ignore conditions can be monitored. It thus provides a real-time means of observing brain activity when the subject is apparently inattentive. The changes in the electrical activity of the brain that occur to physical stimuli or as a result of psychological events or states (such as attention) are called evoked potentials (EPs). Evoked potentials are obtained by recording repeated brief segments or "sweeps" of EEG activity prior to and following stimulus presentation. A sweep typically begins a brief time before stimulus presentation and continues for some time following it. The pre-stimulus period is used to form a "baseline" from which the post-stimulus EP is measured. While EPs provide a powerful method to monitor cognitive processing, they do have a major limitation: the changes in the brain's activity are usually very small and are not visible in the ongoing, random background EEG (Picton et al., 1995). Signal averaging techniques

are used to overcome this problem. They permit the extraction of the small amplitude evoked potential from the background EEG. The brain's response is "time-locked" to the stimulus and is assumed to be constant. The amplitude of the ongoing EEG is assumed to be random. Sometimes it is negative-going; sometimes it is positive going. The summation of random negative and positive activity tends toward zero. In contrast, the average of the constant amplitude evoked potential is that constant. By averaging a sufficient number of sweeps or "trials", most of the background EEG activity therefore averages out, leaving behind the brain's constant response to the stimulus (plus some residual EEG "noise"). The number of trials required to clearly distinguish the EP signal from the background EEG noise is dependent on both the size of the signal and the size of the EEG. Thus, the smaller the signal and the larger the EEG, the greater the number of trials that need to be averaged. For example, extracting an EP signal whose amplitude may be less than 1 μV embedded in a background EEG activity as large as 200 μV or more can be quite time-consuming. In this example, the signal-to-noise ratio (S/N) is 1:200. A much larger number of trials would need to be averaged when the S/N is 1:200 compared to when it is 1:10. Averaging reduces the background noise such that residual noise is inversely proportional to the square root of the number of repetitions. This is known as the "square-root" rule of averaging. Thus, if a researcher wishes to double the signal-to-noise ratio (i.e., to make the EP twice as clear in the

background EEG) he/she needs to present 4 times (2^2) rather than 2 times the number of trials. In the above example, thousands of epochs may have to be averaged in order to reliably distinguish the signal from the background noise.

Evoked Potential Methodology

Evoked potentials are the time-locked changes in the brain's electrical activity that are "evoked" by an external physical stimulus, or "emitted" by the brain as it makes a decision or prepares to initiate a response (Picton and Hink, 1974; Picton et al., 1984; Picton et al., 1995). These scalp-recorded potentials are unique in that they allow for the measurement of discrete neuronal activity before, during and after sensory stimulation, cognitive processing and/or behavioural response preparation.

Evoked potentials may be described as "exogenous" if they are mainly affected by the physical attributes of the eliciting stimulus (Donchin et al., 1978). Exogenous EPs are not affected by the psychological relevance of the stimulus or the psychological state of the subject. Thus, manipulating the intensity of the stimulus may affect an exogenous EP. However, manipulating a subject's level of attention will not alter the exogenous waveform. Emitted, or cognitive EPs may be considered "endogenous" if they are mainly affected by the psychological significance of the stimulus to the subject or by the psychological state of the subject such as their level of attention (Hillyard et al., 1973; Donchin et al., 1978). Because

endogenous components are dependent on psychological events, they are commonly referred to as "event-related" potentials or "ERPs". Endogenous potentials are unaffected by the physical characteristics of the stimulus. Attention is generally considered to be a psychological state. Thus, manipulation of attention will affect endogenous but not exogenous potentials since the psychological state of the subject has been altered rather than the physical characteristics of the eliciting stimulus.

Evoked potentials represent the activation of neurons from one or more intra-cerebral generators which summate temporally and spatially. They are manifested as positive and negative polarity deflections (or "components") at the scalp. Evoked potentials do not necessarily reflect individual cerebral events but may be composed of two or more subcomponents (Näätänen, 1990). Recent evidence indicates that cognitive potentials may be comprised of multiple cerebral generators or processes which overlap in time and space, and which reflect to varying degrees, more basic mental functions (Näätänen and Picton, 1987). Although composite EPs provide convenient peak deflections from which to measure amplitude and latency values, subcomponent processes contributing to these peaks can typically be inferred only through specific experimental manipulations (Näätänen, 1990).

The definition of a "component" remains somewhat equivocal. Donchin et al. (1978) define an EP component as being "a source of controlled observable variability". Näätänen and Picton (1987)

however, define an EP 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". While these two interpretations of what constitutes an EP component do overlap, the definition proposed by Donchin et al. (1978) relates more to experimental manipulations of the EP components. Experimental manipulations must affect independent components differently, while the definition provided by Näätänen and Picton (1987) limits EP components to localized physiologic activity. The independence of a component can only be established when intra-cranial generators can be shown to be different. The more recent definition provided by Näätänen and Picton (1987) will be used throughout this thesis.

Components of the Evoked Potential

Evoked potentials have been elicited by stimuli in all modalities. Indeed it can be demonstrated that an EP can be elicited by the omission of a physical stimulus in a regular train of events. This thesis will examine the effects of loss of consciousness during sleep onset on *auditory* EPs. The control of presentation of visual stimuli to the retina is problematic during sleep since the eyes are, of course, closed. Auditory stimuli are therefore typically used in sleep research since input to the ear can be carefully controlled through the use of headphones or ear inserts. A number of older studies employed

loudspeakers placed beside or over the sleeper's head. Loudspeakers have not been commonly used in more recent research since constancy of stimulus input cannot be assured due to head movement during the night.

The auditory EP waveform consists of a series of positive and negative voltage deflections whose peak latencies range from a few ms to as long as 800 ms or more. Classification and labelling of EPs is somewhat arbitrary. In addition to being classified as exogenous or endogenous, components are also classified according to their peak latency as being either "early" (short-latency, occurring from 0-12 ms), "middle" (mid-latency, occurring from 12-50 ms) or "late" (long-latency, occurring from 50-800 ms) (Davis, 1976).

Short-Latency Evoked Potentials

The very short latency positive polarity components occurring between 0 and 12 ms post-stimulus are labelled using Roman numerals as peaks I through VI (Jewett and Williston, 1971). These components represent evoked activation of neurons in the peripheral auditory nerve and the brain stem subcortical auditory pathways and nuclei. They are thus collectively called the brain stem auditory evoked potential (BAEP). Most labs, using a variety of experimental paradigms, have found the BAEP to be markedly affected by manipulation of the physical parameters of the eliciting stimulus such as by its modality, intensity and/or rate of presentation and minimally affected by cognitive factors

such as subject's level of attention (Picton et al., 1981; Connolly et al., 1989; Hackley et al., 1990). Lucas (1980, 1981) did, however, did find a difference in the amplitude and latency of peak V as a result of manipulating the subject's level of attention although this effect has not been replicated (Picton et al., 1981; Connolly et al., 1989; Hirschorn and Michie, 1990). Studies which investigated the effect of sleep on the BAEP have found this early series of positive deflections to remain relatively unaltered (Amadeo & Shagass, 1973; Osterhammel et al., 1985; Campbell & Bartoli, 1986; Deacon-Elliot et al., 1987; Bastuji et al., 1988) or show only relatively small changes (Stelmack et al., 1993). The stability of the BAEP during sleep was found regardless of stimulus intensity or rate of presentation (Campbell & Bartoli, 1986; Deacon-Elliot et al., 1987). More recently, evidence has indicated that selective attention may alter the acoustic emissions in the human cochlear, suggesting that attention can have an effect as early as the cochlear receptor prior to processing within the central nervous system (Giard et al., 1994). In reviewing studies on the modulating effects of attention on the BAEP, Näätänen (1992), however, concluded "that the weight of the available evidence clearly indicates that the (BAEP) as recorded from the scalp is not modulated by selective attention".

Mid-Latency Evoked Potentials

The mid-latency components, occurring between 12 and 50 ms post-stimulus, are labelled using a combination of upper- and lower-case letters denoting the polarity of the potential (either "N" for negative or "P" for positive), and the order in which it occurs relative to the other mid-latency components (0, a or b). Thus, "Na" would refer to the second negative deflection within this time period. Mid-latency components perhaps originate in the thalamus and primary auditory cortex (Picton et al., 1974; Picton et al., 1984).

The mid-latency components are also largely determined by the physical parameters of the eliciting stimulus (Picton and Hillyard, 1974; Picton and Hink, 1974; Picton et al., 1984; Hackley et al., 1990). As such, these pre-50 ms responses are usually designated as "stimulus bound" or "exogenous" (Sutton et al., 1965; Donchin et al., 1978). There is some evidence that mid-latency EPs can be altered by tasks in which unattended, irrelevant stimuli are physically quite distinct from the attended, relevant stimuli. Woldorff et al. (1987) randomly presented tones rapidly to subject's left (5000 Hz) and right (3400 Hz) ears respectively. Subjects were instructed to detect with a button press, the occasional softer tone pip presented to the designated ear. Woldorff et al. found an enhanced positivity occurring between 20 and 50 ms post-stimulus in EPs recorded under the Attend condition. This enhanced positivity occurred at about the same time as the Pa peak of the mid-latency response,

possibly reflecting activity in or around the primary auditory cortex. These results were replicated by Hackley et al. (1987). In a more detailed report, Woldorff and Hillyard (1991) indicated that these short-latency changes supported an "early-selection" hypothesis. As such, easy-to-detect irrelevant information may be gated relatively early in the processing of auditory stimuli. Furthermore, the Nb component of the mid-latency response has been reported to become somewhat delayed and/or attenuated with the onset of sleep (Osterhammel et al., 1985) although these results have not been consistently found (Erwin and Buchwald, 1986).

The rate of stimulus presentation also appears to have a modulating effect on the EP recorded during attentive states. When stimuli are presented rapidly (every 25 ms) a 40 Hz evoked response was found to become attenuated during sleep, a period when subjects are obviously not attentive toward the stimuli (Linden et al., 1985; Jones and Baxter, 1988). Analogous to studies of selective attention whereby stimuli presented slowly are difficult to ignore, stimuli presented at speeded rates might be rejected early in the nervous system. While there exists some evidence for a selective attentional effect on the mid-latency auditory EPs, it remains unclear as to whether this reflects a modulation of an exogenous sensory component or an overlapping endogenous component.

Differences in task difficulty and rates of stimulus presentation may account for some of the ambiguous research

findings. Unfortunately, mid-latency potentials tend to be small and variable, and thus are often difficult to identify (Vaughan and Arezzo, 1988). Furthermore, the difficulty of identification and analysis is compounded by overlapping myogenic potential artifact generated by post-auricular musculature (Picton et al., 1974; Vaughan and Arezzo, 1988). It is possible that attention may alter muscle tonus rather than the actual brain responses.

Long-Latency Evoked Potentials

Long latency EPs occurring after 50 ms post-stimulus are often labelled according to their polarity and peak latency. Since peak latencies may vary under different recording conditions and among different individuals, the peak is generically defined by its typical latency. Thus, N100 would refer to a negative deflection occurring approximately 100 ms post-stimulus. There are problems with this labelling method. The peak latency of a component is usually delayed for older subjects. Also, different experimental conditions might cause a peak latency to be significantly delayed. Thus a late positive wave, P300, may occur as early as 300 ms or as late as 600 ms dependent on the ease of stimulus classification and/or the age of the subject. However, whether P300 occurs at 300 or 600 ms, it is assumed to reflect the activity of the same intra-cranial generators. To avoid labelling the same potential as having different latencies under different experimental conditions or in different subject populations, another system of nomenclature has

been developed replacing the approximate peak latency by a sequential numbering of the peak deflections. Thus a positive wave, P180, might also be labelled as "P2" since it occurs after P1 (latency about 50 ms) and before P3 (latency about 300 ms). There are also problems with this labelling system. After the initial labelling has been standardized, subcomponents may subsequently be found to contribute to or be superimposed upon this EP deflection. In the 1970s, N100 was also labelled as N1. Later, additional negativities in this latency range were discovered. Rather than re-labelling the standardized peaks, these newly discovered subcomponents are labelled by adding a lower-case letter in a hierarchical fashion to the previously established component. Thus, the N1 deflection has been subdivided into the N1a, N1b and N1c subcomponents (McCallum & Curry, 1979) although N1a and N1b have not always been distinguishable (Perrault & Picton, 1984).

Long-duration "slow potentials" are difficult to label since they may not have a distinctive peak. They have been labelled according to their presumed psychological function. These include the mismatch negativity (MMN) (Näätänen et al., 1986), the processing negativity (PN) (Näätänen and Michie, 1979) and the contingent negative variation (CNV) waveforms (Walter et al., 1964). These potentials are considered as "cognitive" or "endogenous" ERPs because they are dependent on discrete task-relevant events requiring mental activity rather than on the physical attributes of the eliciting stimulus.

Late Auditory Evoked Potentials

The first series of long-latency auditory EPs includes the P1, N1 and P2 components. P1, peaking at approximately 50-80 ms post-stimulus appears maximal over central areas of the scalp (Goff et al., 1969, 1977; Picton et al., 1974; Wolpaw and Wood, 1982). N1, peaking at approximately 100 ms post-stimulus, is recorded maximally over the fronto-central areas of the scalp (Picton et al., 1974; Wood and Wolpaw, 1982; Alho et al., 1986; Woods and Clayworth, 1987). Wolpaw and Penry (1975) suggested that the scalp-recorded N1 is comprised of multiple generators. They observed that a "T-complex" wave had a positive peak at about 105 ms (labelled "Ta") and a negative peak at about 150 ms (labelled "Tb"), which overlapped a separately occurring vertex N1 response peaking at about 120 ms. The T-complex was largest over the temporal areas of the scalp and was thought to be generated in the secondary auditory cortex whereas the N1 response reflected a nonspecific activation of the frontal cortex. McCallum and Curry (1979, 1980) identified three separate peaks in the latency range of the N1 and labelled them as N1a, N1b and N1c. N1a was maximally recorded from temporal and frontal-pole electrodes and had a mean peak latency of 75 ms. N1b was maximally recorded at central scalp sites and had a mean peak latency of 105 ms. N1c was recorded maximally from the temporal electrode sites and had a peak latency of 130 ms. Perrault and Picton (1984), however, were unable to dissociate the N1a and N1b described by McCallum and Curry (1979). Perrault and Picton

suggested that these two subcomponents represent the same cerebral process which may be overlapped by a positive wave such as the Ta component described by Wolpaw and Penry (1975). Wood and Wolpaw (1982) found three successive electrical fields in the latency range of the auditory N1 potential occurring at 78 ms (frontally negative and temporally positive), at 88 ms (frontally negative), and at 115 ms (temporally negative). Wood and Wolpaw suggested two possible source configurations which could account for the N1 distribution they recorded. The first configuration located a source in the supra-temporal plane (as proposed earlier by Vaughn and Ritter, 1970) with additional overlapping activity from other underlying source(s). The second configuration identified widespread cortical activity with overlapping temporal activation as suggested by Wolpaw and Penry (1975).

Scherg and Picton (1991) have indicated that there are at least two bilateral source dipoles which actively contribute to the N1 potential. Evidence for this also comes from the work of Scherg and von Cramon (1985; 1986a; 1986b), who used source localization techniques to model the N1 negativity occurring from 75 to 200 ms post-stimulus. Two dipoles in each temporal lobe provided the best mathematical fit to explain the variance in the scalp-recorded activity. One, a tangential source, located in the auditory cortices on the superior aspect of the temporal lobe, had a vertical orientation toward the frontal lobe. It possibly represented the source of N1b and could explain why it was maximum over fronto-central areas of the scalp. The second

current dipole, located in the auditory association cortices of the superior temporal gyrus, was oriented radially (horizontally). It possibly represented the source of N1c and could explain why it was maximum over temporal areas of the scalp.

Näätänen and Picton (1987), in a now classic review, have suggested the composite N1 is made up of as many as six sub-component processes reflecting both exogenous and endogenous characteristics. Each sub-component can be defined by its unique electrical field and relationship to various experimental manipulations (Näätänen, 1990). The first three subcomponents are believed to contribute to the "genuine" N1 reflecting the *exogenous* nature of this potential (Näätänen and Picton, 1987). These sensory subcomponents are elicited from 80 to 150 ms after stimulus onset and overlap to form the vertex N1 potential. In keeping with the nature of exogenous components, they can be altered by manipulation of many physical attributes of the stimulus including: ear of presentation (Perrault and Picton, 1984); stimulus intensity (Beagley and Knight, 1967; Picton et al., 1977); tonal frequency, inter-stimulus interval (Davis et al., 1966; Picton et al., 1977); and/or duration of stimulus presentation (Picton et al., 1977).

One of Näätänen and Picton's subcomponents (probably the N1b of McCallum and Curry, 1979), is maximum over fronto-central areas of the scalp and peaks at about 100 ms post-stimulus. It is believed to be generated by bilateral, vertically oriented

tangential dipoles originating in the supra-temporal plane of the auditory cortex (Vaughan and Ritter, 1970; Scherg and Von Cramon, 1985, 1986a, 1990; Richer et al., 1989; Bertrand et al., 1991). Mathematical modelling of magnetic recordings (MEG) have also confirmed the existence of this tangential dipole in the superior temporal cortex (Elberling et al., 1980; 1981; Hari et al., 1980). Moreover, N1b cannot be elicited in patients that have lesions in this particular region (Scherg and von Cramon, 1986a; 1986b).

An additional N1 sub-component is recorded maximally at the mid-temporal scalp regions and appears as a biphasic T-complex wave with a positive wave at 100 ms and a negative wave at 150 ms (Wolpaw and Penry, 1975). This is probably the N1c of McCallum and Curry (1979). Electrical scalp potential recordings of this late negativity could be modelled by a radially-oriented dipole in the temporal lobe. It is believed to reflect activity in the superior temporal gyrus of the auditory association cortex (Wolpaw and Penry, 1975; Scherg and Von Cramon, 1985, 1986a, 1986b, 1990; Scherg et al., 1989; Bertrand et al., 1991; Scherg and Picton, 1991; Giard et al., 1994). Apart from the source modelling of the scalp electrical activity in this latency period, there is little additional independent evidence to support the existence of this dipole. Magnetic recordings are not, unfortunately, sensitive to radially oriented dipoles (Baule and McFee, 1965).

A third N1 subcomponent is much more controversial. This

subcomponent was thought to represent widespread activation recorded maximally from the vertex, with a peak latency of about 100 ms (Velasco et al., 1985; Velasco and Velasco, 1986). Näätänen and Picton (1987) have described this "non-specific" component as being related to the detection of infrequently presented stimuli. Evidence comes primarily from a study in which stimuli were delivered at relatively slow rates (Hari et al., 1982). Hari et al. presented tones binaurally to subjects varying the ISI from 1 to 16 s. Simultaneous magnetic and electrical responses were recorded from all subjects. At intervals of less than 4 s the vertex and frontal amplitudes were approximately equal for both magnetic and electrical responses. When ISIs were longer than 4 s, only the vertex-recorded electrical potential was further augmented. Hari et al. suggested that the N1 magnetic potential was likely generated by current dipoles located in the supra-temporal planes (the N1b response), and reasoned that "some additional sources are activated during infrequent stimulation" to explain the increase in the vertex N1 electrical potential to stimuli presented with longer interstimulus intervals (ISIs). They thought that the additional activity reflected by the augmented electrical N1 (elicited by stimuli with longer ISIs), was related to the orienting response. This activity may arise from a radially-oriented dipole located in the region of the vertex, and which is activated by relatively infrequently occurring stimuli.

Mapping of the N1 Evoked Potential

Evoked potential components are often distinguished on the basis of their scalp topography. Components whose scalp topography vary must have different intra-cranial generators. Many authors, therefore, record ERPs from multiple scalp electrodes, from as few as 12-14 in older studies to as many as 128 in more recent studies. Maps of the component of interest are usually computed to provide a graphical summary of the data. The amplitude of an ERP component is measured at each electrode site. Amplitudes in spaces between the electrodes are mathematically computed through interpolation. Since many maps are made up of a matrix of perhaps 64 x 64 measures, a large amount of interpolation is required. Voltage distribution maps do, however, provide a convenient graphic image of the maxima and minima of a peak component's scalp topography.

Scalp-recorded electrical potentials show a smeared representation of currents originating within the brain (Picton et al., 1995). This is a result of the diffusion of current as it is volume-conducted from its source through to the to the scalp surface. The diffusing effect that the subcutaneous tissue has on the ERP signal, as it appears on the scalp, may be reduced by computing the second spatial derivative of the scalp-recorded activity. This is equivalent to applying a high-pass filter to the potential fields. The resulting current source density (CSD) map provides an estimate of the effective sources (positivity) and sinks (negativity) of radial current. CSD maps are often used

to distinguish between scalp topographies that result from a deep-seated dipole generator and those that result from a more superficial, near-generator. CSD maps of near-generator sources are represented as well-delineated focal activity localized over certain brain regions whereas deep-seated dipole sources produce only widespread, generalized activity (Pernier et al., 1988).

Giard et al. (1994), in an attempt to provide evidence of the "additional activity" of the frontal components as described by Hari et al. (1982), recorded scalp activity from 24 electrode sites. They used spline interpolation and CSD mapping techniques to assess the topography of the N1 potential. Giard et al. found clear evidence that both frontal and temporal components contributed to the N1 ERP. Unlike Hari et al., they indicated that the frontal components can be elicited even with very short ISIs of 500 ms. The earlier Scherg and von Cramon (1986a), Scherg et al. (1989) and Scherg and Picton (1991) articles also did not report frontal dipole sources when relatively short (1-2 s) ISIs were used. In these studies, the EEG was recorded from 14-16 electrode sites. Giard et al. indicated that a higher spatial electrode resolution is required to observe the frontal source activity. When they restricted their analysis to a 17 channel array, the frontal sources were not apparent. Furthermore, Giard et al. pointed out that the method of computing the map of the electrical data can have a critical role. When the usual spherical spline voltage distribution maps were computed, the frontal component was not evident, even when a 24 channel

electrode array was used. However, when CSD maps were computed, a bilateral frontal current over the left and right fronto-central regions emerged.

A number of possible generator sites were mentioned. Giard et al. speculated that the frontal currents could reflect activity of the motor cortex, the supplementary motor area of the medial aspect of the superior frontal gyrus and/or the singulate gyrus (Hari et al., 1982; Näätänen and Picton, 1987). These areas are consistent with the findings from intracranial recordings in animals (Arrezo et al., 1975) and with lesions in frontal lobe patients (Knight et al., 1980). Näätänen and Picton (1987) suggest that these cortical regions may be under the influence of the reticular formation and the ventral lateral nucleus of the thalamus to produce non-specific orientation toward infrequent stimuli leading to conscious awareness.

Recently it has been suggested that there may in fact be two frontal ERP components active when the ISI is greater than 8 s (Giard et al., 1994; Alcaini et al., 1994). These frontal components may reflect attention toward stimulus detection (previously attributed only to the supra-temporal mechanism - see Verbaten, 1990) and non-specific aspects of auditory processing. Alcaini et al. (1994) presented auditory stimuli every 1, 2, 4, 8, 16 or 120 s, thus replicating the original Hari et al. (1982) rates of presentation, and adding an additional 2 min ISI. At the faster rates of presentation, CSD mapping revealed a frontal sink, similar to that observed by Giard et al. (1994). However,

at the longer 8, 16 and 120 s ISIs, an additional late N1 peaking at approximately 140 ms was observed which had a more central topography than the frontal negativity found by Giard et al. (1994). CSD analysis of this later negativity also pointed to a frontal current. Alcaini et al. speculated that the frontal component described by Giard et al. (1994) is a new obligatory component of the N1 ERP and the additional negativity found in their study with longer ISIs (4 or more s) probably corresponds to the "non-specific" orienting component described by Näätänen and Picton (1987).

The remaining three subcomponents occur independently of the sensory N1 and are altered by cognitive processes such as memory and attention. These endogenous subcomponents often summate with the sensory N1 to augment its amplitude. The fourth subcomponent is called the "mismatch negativity" (MMN) and is thought to reflect an automatic, rapidly decaying neuronal comparison of the physical features of two consecutive stimuli (Näätänen et al., 1986, 1987a, 1987b, 1989a, 1989b). Since the MMN is not a focus of this thesis, it will not be discussed further. The fifth subcomponent known as processing negativity (PN) reflects the differential processing of attended auditory stimuli (Näätänen, 1982; Näätänen and Picton, 1987). PN (and the related "Nd" wave measuring the difference in negativity between the attended and unattended stimuli) are particularly relevant to this thesis and will be discussed in greater detail later.

The final subcomponent of the N1 has been labelled "the

attention supervisor" (Näätänen and Picton, 1987). While closely related to PN, this potential has a longer time span than that of the PN wave and is believed to be generated in the anterior frontal cortex following activation of the auditory sensory areas (Näätänen and Picton, 1987). The attention supervisor is thought to play a role in the regulation of auditory information processing (Näätänen and Picton, 1987). There is little evidence to support the existence of this negativity and it remains poorly understood.

The "P2" wave, peaking at approximately 200 ms post-stimulus has received much less attention in the literature than N1. Like N1, it may also be comprised of specific and non-specific components (Vaughan et al., 1980). P2 is usually investigated concurrently with the N1 potential although they have different scalp distributions. P2 is centrally distributed on the scalp with a slight right hemisphere dominance (Paavilainen et al., 1991). Increased attention may actually decrease the amplitude of P2 through the overlapping and summating effects of the Processing Negativity (Näätänen and Picton, 1987).

The second major negative wave, labelled "N2", is recorded maximally over fronto-central electrode sites. It is most commonly elicited in the alert wakeful subject using an "oddball-paradigm". This paradigm requires subjects to detect infrequently occurring rare stimuli presented randomly within a train of frequently occurring "standard" stimuli (Ritter and Vaughn, 1969). This waking N2 (to distinguish it from an N2 recorded

during sleep), occurs 250-350 ms post-stimulus and becomes larger when physical differences between the rare and frequent stimuli are smaller. Fitzgerald and Picton (1983) suggested that subjects must expend greater processing "effort" to distinguish frequent from rare stimuli when differences between the stimuli are small. It is this processing effort that is reflected in the amplitude of N2. The waking N2 appears, however, to be a composite of two separate subcomponents labelled as "N2a", having a more frontal distribution, and "N2b", having a more central distribution (Näätänen et al., 1982). N2a is believed to reflect the automatic attention component elicited whenever a rare, unexpected stimulus occurs independently of the subject's attention. Thus, N2a may be an extension of the MMN component found to contribute to the N1 response (Näätänen et al., 1982; Fitzgerald and Picton, 1983). N2b is believed to reflect the extent of conscious effort required to differentiate rare from frequent stimuli (Fitzgerald and Picton, 1983).

A large N2 can also be elicited in the sleeping subject. For this reason, it is labelled the "sleep N2" to distinguish it from the N2 observed in waking subjects (Näätänen and Picton, 1987). Unlike the case for the waking N2, a simple repetitive stimulus can elicit a large N2 in sleeping subjects. Unlike the waking N2, the sleep N2 is recorded maximally from central scalp sites (Côté et al., 1996). The sleep N2, occurring approximately 350 ms post-stimulus may reflect, at least in part, the averaging of vertex sharp waves or occasional high amplitude K-Complexes which can

also be evoked in sleep by periodic auditory stimulation (Oswald et al., 1960; Näätänen, 1982; Bastien and Campbell, 1994; Harsh et al., 1994; Winter et al., 1995; Côté et al., 1996; Colrain, personal communication).

A late positive component, the "P300" or "P3", occurring approximately 300 ms post-stimulus is recorded maximally over the parietal areas of the scalp (Vaughn and Ritter, 1970; Donchin and Pritchard, 1981; Coles, 1988; Picton, 1992), and like the waking N2 which precedes it, is most often elicited during the oddball paradigm (Vaughn and Ritter, 1970; Pritchard, 1981; Donchin and Coles, 1988; Picton, 1992). The task for subjects in the oddball paradigm is to consciously detect infrequently occurring rare "targets" presented randomly within a train of frequently occurring standard "non-targets" (Ritter and Vaughn, 1969). The amplitude of P3 has been shown to be inversely related to the probability of target presentation (Duncan-Johnson and Donchin, 1977; Campbell et al., 1979). In the usual oddball task, subjects are asked to either keep a running mental count of the number of "target" occurrences or to button press upon their detection. The latter has the advantage that in addition to providing a reliable index of accuracy of detection, a measure of the speed of decision-making, the subject's reaction time (RT), can also be computed. Importantly, in both methods, subjects make a *conscious* detection of the target. The appearance of a P3 wave is thus a reflection that (a) the stimulus was presented infrequently and (b) the subject was consciously aware of its presentation. The

"standard" frequently occurring stimulus will elicit only a small amplitude P3 even if the subject is asked to make an overt response to it. Thus, although P3 requires a conscious detection of the stimulus, an additional requirement is that the stimulus to-be-detected occurs infrequently. If subjects are asked to ignore all stimuli by directing their attention elsewhere (such as by reading a book) P3 will not be elicited (Hillyard et al., 1973, Squires et al., 1975a; Donald and Little, 1981), even if the stimulus only occurs infrequently. Thus, while P3 is a good measure of conscious detection of rare events, it is a poor measure of what might be considered general "consciousness". P3 will not be elicited in fully awake and conscious subjects if the stimulus is presented frequently (even if it is "consciously" detected) or if the subject ignores or fails to detect it.

There are, however, circumstances in which a subcomponent of the P3 wave can be elicited in apparently inattentive subjects. When subjects are ignoring stimuli, a highly relevant and novel, unexpected stimulus may elicit an earlier, smaller and more frontally distributed P3 (Squires et al., 1975b; Ruchkin et al., 1990). This automatically-elicited P3 occurring independently of task demands, is labelled "P3a" to distinguish it from the longer latency, more attention-related parietal "P3b".

Evoked potentials such as the waking N2 and P3 appear to reflect the psychological state of the subject and/or the information content of the eliciting stimuli independently of their physical characteristics (Donchin et al., 1978; Campbell,

1985; Picton et al., 1995). The earlier vertex P1-N1-P2 response however, appears to be affected by both the sensory aspects of the eliciting stimuli (Davis et al., 1966; Picton et al., 1978) and also the cognitive state of the subject (Näätänen and Picton, 1987; Näätänen, 1990).

Attention-Related Evoked Potentials

This thesis is mainly concerned with attention-related EPs. In studies of attention, processing when the subject is attentive is compared to processing when the subject is inattentive (and presumably not attending to the stimuli). The auditory P1-N1-P2 complex is among the shortest latency EPs to be affected by the subject's level of attention. In early (1950s and 1960s) evoked potential studies of selective attention, the to-be-ignored and the to-be-attended stimuli were usually presented in a predictable alternating order. In such paradigms, subjects might be asked to make a response to relevant (attended) stimuli and to ignore (not respond to) the irrelevant. The problem with this paradigm is that the subject must obviously attend to and process the to-be-ignored stimulus until it can be detected as "irrelevant". Presumably, subjects would have to process the "irrelevant" stimulus to know it is in fact irrelevant (i.e., does not require a response) and can thus be "ignored". The results of many of these early studies were, not surprisingly, equivocal (Davis, 1964; Spong et al., 1965; Wilkinson and Morlock, 1966). Even when studies did find a difference in EPs to

"attended" and "ignored" stimuli, the results could be explained by factors other than attention. Subjects could anticipate and prepare for the onset of the predictable relevant stimulus. Differences in anticipation and preparatory processes occurring before the onset of the relevant stimulus could also explain the results.

In other studies, subjects were asked to attend to the stimuli in one condition, and to ignore them in a second condition. Although attentional effects could have contributed to these findings, the experimental design was confounded by possible differences in arousal or alertness between the Attend and Ignore conditions (Näätänen, 1967). It was possible that in the Attend conditions subjects were both more attentive and more aroused.

In order to remove the predictability of stimulus occurrence, Näätänen (1967) presented to-be-attended and to-be-ignored stimuli in a random order and with an interstimulus interval (ISI) that varied between 1 and 3 s. There were no significant differences between the vertex response recorded to the relevant (attended) and irrelevant (ignored) clicks. This study was replicated by Hartley (1970) who also failed to find EP differences between attended and ignored stimuli. Hartley suggested that the slow rate of stimulus presentation may have allowed subjects to passively attend to both the to-be-attended and to-be-ignored channels without any effect on performance.

Methods of measuring the amplitude of EPs may have also

inadvertently produced contradictory results. Many studies at this time employed a "peak-to-peak" measurement technique. N1-P2 was measured as the distance (or difference) from the maximum peak of N1 to the maximum peak of P2. Peak-to-peak measurement has three major disadvantages. An implicit assumption is made that the two peaks reflect the same intra-cranial source activity. In the case of N1-P2, more recent findings indicate this is almost certainly not the case. A second problem is that peak-to-peak measurement cannot be used to determine the effects of experimental manipulations on one peak independently of the other. Thus, if attention has an effect on the composite N1-P2, it cannot be determined if this is due to an effect on N1 or on P2 or on both N1 and P2. Finally, and perhaps most importantly, the experimental manipulation may result in the attentional process being extended for a long period of time. The brain activity associated with this additional, long lasting processing may overlap (and thus summate) with both evoked potentials of interest (N1 and P2 in this case). As will be discussed in a later section, this seems to be precisely the effect of attention. Attention to a particular channel may result in the elicitation of a long-lasting negative polarity slow wave that overlaps and summates to both N1 and P2. N1 thus appears to be more negative while P2 appears to be less positive (i.e., also more negative). A negative constant is thus added to N1 and P2. However, the peak-to-peak measurement subtracts one peak amplitude from the other. It thus *removes* the constant negativity

that was *added* by the additional processing during attention. Therefore, when the subject is attentive, N1 may appear to increase in amplitude while P2 decreases. When the subject is inattentive, N1 may decrease in amplitude while P2 increases. In both Attend and Ignore conditions, while very clear differences exist, peak-to-peak amplitudes may well be identical! Peak-to-peak measurement might therefore cancel out the true effects of attention.

For these reasons, more recent EP research has employed a baseline-to-peak measurement technique. The evoked potential "sweep" begins prior to stimulus presentation. The average of this prestimulus activity is used to form a "baseline" since it is assumed to reflect random brain activity that is independent of the yet-to-be presented stimulus. Prior to the advent of mini-computers and more recently, microcomputers, the EEG sweep was "triggered" by the onset of the stimulus. Since pre-stimulus baseline data could not be collected, researchers were forced to rely on peak-to-peak measurement. An advantage of baseline-to-peak measurement is that peaks such as N1 and P2 can be measured independently. Experimental effects can thus be determined for N1 and P2.

Wilkinson and Lee (1972) are generally credited with the development of an optimal methodology for the study of the effects of selective attention. In different conditions, binaural tones were presented with an intensity of either: 61, 72 or 78 dB SPL. Stimuli within each series consisted of a single to-be-

attended tone and two to-be-ignored tones. The Attended and Ignored tones varied in pitch. The subject's task was to count a different tone (the relevant tone) in each series. Tones were presented randomly with a variable ISI of between 300 and 1760 ms (average of 673 ms), a rate of presentation that was much more rapid than in previous studies. Moreover, the randomized ISI precluded prediction of the timing of the occurrence of the next stimulus presentation. The probability of each tone occurring within a run was approximately equal. The procedure was then repeated at the other two intensities. Wilkinson and Lee failed to find an effect of selective attention on the amplitude of either N1 or P2. This study has been criticized by Hillyard et al. (1973) who argued that since all stimuli (whether relevant or irrelevant) are presented to the same binaural channel, subjects could not form a "selective" set permitting the further processing of attended, and the rejection of unattended stimuli. As with previous studies, it would appear that subjects also had to extensively process the to-be-ignored stimuli in order to determine that they were irrelevant. The failure to find N1-P2 differences could be because the N1-P2 peaks are insensitive to manipulations of attention or alternatively that both relevant and irrelevant stimuli were, in fact, extensively processed.

In a now classic study, Hillyard et al. (1973) employed a dichotic listening task in which frequent and rare tones (differing in pitch) were presented rapidly (every 200-400 ms) and randomly to both left and right ears. Subjects were

instructed to selectively attend to stimuli in one ear and detect (with a button press) the occasional target tone of a slightly higher pitch while ignoring all competing stimuli presented in the opposite ear. An attention set was thus set up, based on ear of delivery. Subjects needed only detect the ear of delivery and no other feature of the stimulus to begin to "gate" the irrelevant stimulus. Thus, the irrelevant stimulus could be rejected quite rapidly in this paradigm. In some blocks of trials, the subject was instructed to attend to their left ear and in other blocks to attend to their right ear. The detection task was quite difficult. Subjects' error rate was approximately 0.20. Thus, the difficulty of the task ensured subjects had to selectively attend to one ear and ignore the other in order to accurately detect the relevant target. Because of the rapid rate of presentation, the subject could not switch between ears and still maintain a satisfactory level of performance (as had been the case in previous studies). This design had another advantage in that it controlled for subjects' level of arousal. EPs recorded from the to-be-attended stimuli could be compared with EPs recorded to the same stimuli when they were to-be-ignored. Differences between Attend and Ignore conditions could not be explained by differential arousal since the subject was simultaneously attending one channel and ignoring the other in the same condition. The requirement of a behavioural response provided an independent measure of attention. A high hit rate was used as evidence that subjects were attentive. Results indicated

that the N1 recorded to attended stimuli were augmented compared to when the same stimuli were ignored. Since identical stimuli were presented in both Attend and Ignore conditions, differences could not be attributed to the physical attributes of the stimuli. The effect could only be explained by the endogenous, psychological effect of attention. This enhancement of the N1 as a result of selective attention has become known as the "N1 effect" (Hillyard et al. 1973; Picton and Hillyard, 1974). Hillyard et al. regarded their finding as support for Broadbent's (1970, 1971) stimulus-set mode of attention. They suggested that subjects were focussing their attention on a specific stimulus set (in this case the ear to which they were attending) in order to further analyse the difference in pitch of the frequent and rare tones. The processing of the auditory stimuli presented in the ear which was to-be-ignored was therefore attenuated relative to the attended channel. This selectivity occurred around 60 ms after stimulus onset, suggesting to the authors that this was a tonically maintained attention set favouring one ear over the other (Hillyard et al., 1973).

Schwent et al. (1976a, 1976b) carried out similar dichotic listening tasks to those used by Hillyard et al. (1973) in order to examine the intrusive effects of the rate of stimulus presentation and stimulus intensity. In their initial study, when stimuli were presented rapidly (mean ISI = 350 ms), N1 was larger to the attended channel compared to when it was ignored (Schwent et al., 1976a). When stimuli were presented slowly (mean ISI =

1920 ms), the amplitude of N1 did not differ between Attend and Ignore conditions. It appeared subjects could not ignore the slowly presented, but irrelevant stimuli. They appeared to be switching (i.e. attending) to both the relevant (to-be-attended) and the irrelevant (to-be-ignored) channels. When stimuli were presented at a moderate rate (mean ISI = 960 ms), N1, as predicted, showed an intermediate effect of attention. In a subsequent study, Schwent et al. (1976b) provided evidence that the N1 attention effect could also be modulated by the intensity of the to-be-ignored stimuli. The attend-ignore N1 difference was larger when stimuli were presented at a low intensity compared to when they were presented at a high intensity. As already mentioned, this inability to ignore either loud stimuli or those presented slowly has been described by cognitive psychologists as "the breakthrough of the unattended" (Broadbent, 1982).

Näätänen (1975) and Näätänen et al. (1978), carried out an extensive review of the literature on EPs and attention. They noted that it was not only N1 that was affected by attention. When N1 became larger in Attend conditions, P2 often became smaller (less positive or more negative). The apparently contradictory effects on N1 and P2 (one becoming larger, the other smaller) were explained by an overlapping endogenous subcomponent called "processing negativity" (PN). Näätänen et al. (1978) suggested that the PN was an endogenous component which was generated by a different cerebral source than the one responsible for either the N1 or P2 components. They hypothesized

that the N1 effect described by Hillyard et al. (1973) may have been a result of the PN rather than a tonic facilitation of a set favouring one ear over the other. Thus, the increase in N1 with attention is not simply due to the fact that the attended channel became physiologically "louder".

In studies of selective attention, the PN occurs for both relevant (to-be-attended) *and* irrelevant (to-be-ignored) stimuli, based on their physical features. The fact that PN also occurs to the to-be-ignored stimulus is critical to the present thesis. All stimuli whether attended or not will elicit some PN. In discussing the fate of the ignored channels, all psychologists agree that they must receive a certain amount of processing in order to be rejected as being irrelevant. Where they disagree is the extent of this processing. Näätänen's model provides an elegant solution to this controversy. Importantly, it must be stressed that the model inherently assumes that even the to-be-ignored stimuli are processed (i.e., attended) at least to a certain extent. The extent of this additional processing may vary from slight to a great deal.

PN may start as early as 20-50 ms post-stimulus and may continue for another 250 ms or more. It is probably generated in the auditory and associated areas of the supra-temporal plane (Kaufman and Williamson, 1987; Näätänen and Picton, 1987). When some stimuli are attended more than others (as occurs during selective attention tasks), the difference in PN between attended and unattended stimuli can be observed as a slow negative

displacement "Nd" wave (Hansen and Hillyard, 1980). The Nd wave is calculated by subtracting the evoked potential elicited by unattended stimuli from the evoked potential elicited by attended stimuli (Hansen and Hillyard, 1980). PN, however, cannot actually be observed in the ERP waveform (since it is a composite of exogenous and endogenous potentials). The waveforms to both attended and unattended stimuli are formed by the summating effects of exogenous potentials such as N1 and P2 (reflecting the physical stimulus), and the effects of endogenous potentials such as the Processing Negativity (reflecting the extent of attentional processing). Since the physical stimulus is identical in both the Attend and Ignore conditions, the subtraction process removes the effects of exogenous processing. The difference waveform (Nd) must therefore reflect only the difference in endogenous, attention processing (i.e., PN). Although PN is a theoretical construct, the difference in PN in the attended and unattended conditions can be observed as the Nd wave. The Nd wave starts later than the PN wave since both attended *and* unattended stimuli are initially processed identically (Näätänen, 1990). Thus, the common initial part of the PN is subtracted out. At this common stage of information processing, Nd is of course at baseline (zero voltage). Only when sufficient information has been accumulated to allow relevant stimuli to be selectively distinguished from (and thus processed more than) the irrelevant, will the Nd wave become visible. Again, this is quite an important theoretical concept. If an unattended channel cannot be

at all ignored (i.e., it is completely intrusive), Näätänen would have to assume that the PN would be identical in both Attend and Ignore conditions. In such a situation, there would be no Nd wave. Nd is thus a *relative* measure of attention, reflecting the *additional* processing that a to-be-attended channel receives relative to when it is to-be-ignored.

Since selective attention can cause the Nd wave to overlap and summate to the P1, N1 and P2 potentials, it may alter these components under the "attend" condition by making them more "negative". The Näätänen thesis (see Näätänen, 1990 for a review) maintains that PN and Nd are independent of the effects of N1. Thus attention is more than an enhancement of N1. For example, while Nd can peak at the same time as N1, it can also peak much later depending on the ease of rejection of the to-be-ignored channel. Hansen and Hillyard (1980) have indicated that Nd peaks at approximately 100 ms if the to-be-attended and to-be-ignored channels are easily distinguished. Indeed, the rising edge of Nd can begin as early as 40-50 ms following stimulus presentation if the to-be-attended and to-be-ignored channels are very distinct. On the other hand, if the two channels are quite similar, it will take longer to reject the to-be-ignored channel. PN to the ignored channel will thus last longer. Since Nd provides a measure of difference in PN between attended and ignored channels, the difference only occurs quite late in processing, well after the peak of N1 and perhaps at the time of P2. Since the peak latencies of N1 and Nd can be independently manipulated,

many authors maintain they must reflect different processes.

Picton and Stuss (1980) have indicated that if the scalp distributions of two EP waveforms are different, then their intra-cranial sources must also be different. In this context, it is important to recall that Näätänen and Picton (1987) claim that independence of EP components can only be determined on the basis of different intra-cranial generators. If the maps of N1 and Nd are different, they must have different intra-cranial sources. If they have independent sources, their functional roles are probably also different. There is now quite good evidence that the maps of N1 and Nd are indeed different. Recent studies have employed multichannel recordings to assess the topographical distribution of the attention effect. Giard et al. (1988) employed a complex selective attention task. They indicated that Nd may be made up of as many as three different sub-components. The first was recorded as a small amplitude (less than 1 μV) fronto-central wave peaking before the actual maximum amplitude of N1, and was described as being frequency specific. Few other laboratories have, however, described this Nd potential. Moreover, Giard et al. (1988) did not find this component in all conditions of their study. The second component has been reported in other studies as the *early Nd* wave (Näätänen, 1982; Hansen and Hillyard, 1984). This Nd peaks at approximately the same time as N1, and like N1 is maximum over fronto-central areas of the scalp. For this reason, Hansen and Hillyard (1984) also labelled it as the central Nd wave. The major difference between N1 and

the early Nd wave is that N1 inverts in polarity at the mastoid, when a nose reference in used, whereas the early Nd does not (Alho et al., 1986; Giard et al., 1988; Teder et al., 1992). Moreover, N1 has a contra-lateral distribution (maximum in the hemisphere opposite to the ear of stimulus presentation) whereas the distribution of the early Nd is more symmetrical. The third attentional negativity appears as a late, small amplitude, frontally distributed waveform. This small, frontal attentional component has also been observed in other laboratories, and has been labelled as the *late Nd* wave (Hansen and Hillyard, 1980; 1984; Näätänen et al., 1981; Okita et al., 1983; Alho et al., 1986; Woods and Clayworth, 1987; Giard et al., 1988; Woldorff and Hillyard, 1991). Importantly, the frontal component cannot be detected in CSD maps, although it is apparent in the spline voltage distribution maps. Since CSD representation reflects generators near the scalp surface, Giard et al. (1988) suggested that the late Nd frontal activity is not generated in the frontal cortex, but rather emerges from deeper sources.

In an extensive review of attention, Näätänen (1990) claims that N1, made up of components 1, 2 and 3, largely reflects an exogenous process and is only affected by the physical qualities of the stimulus. Näätänen and Picton suggest "... these "true" components of the auditory N1 wave ... are largely determined by the physical characteristics of the stimulus and by the general state of the subject ... [Other] components in the latency region of the N1 ... are related more to memory and cognition than to

stimulus and state, and which we shall not classify as "true" N1 components" (Näätänen and Picton, 1987, p.386-387). Nd is, thus, not a true N1, but rather a reflection of the endogenous processes.

There is however a flaw in this line of reasoning. Maps of N1 and Nd assume that each reflects independent processes. However, the fact that the peaks of N1 and Nd can be dissociated does not mean that at least a portion N1 cannot be explained by the endogenous Nd process. Critical to this argument is that the subtraction process removes the common influences of the physical stimulus (since this stimulus is identical whether it is attended or ignored). The subtraction process also removes common endogenous influences. To the extent that a stimulus cannot be ignored, the PN to the relevant and irrelevant stimulus will be identical. Subtracting attended and ignored ERPs cancels this common endogenous PN, leaving only the additional PN that the attended channel receives. This subtraction process therefore removes common exogenous *and* endogenous processes. For this reason, it is not possible to dissociate the exogenous N1 from the endogenous Nd. Claims that N1 and Nd are, in fact, independent processes based on their differential scalp distributions make the error of assuming that Nd is an absolute rather than a relative process.

In early studies of attention, N1 did not differ between Attend and Ignore conditions when stimuli were loud or presented at a slow rate (Schwent et al., 1976a; 1976b). This could be

because the stimuli were difficult to ignore. In such cases, PN would be identical in Attend and Ignore conditions (in actual fact, PN was different, but not until well after the peak of N1). An exogenous interpretation can also be used for the Schwent et al. results. Loud stimuli and slow rates of presentation elicit larger amplitude N1s. Subtracting the Ignored from the Attended waveforms would result in an Nd at baseline level (i.e., zero voltage). This could be due to the removal of a common endogenous influence or a common exogenous influence or both. In order to dissociate exogenous (sensory) from endogenous (attention) influences requires a condition in which the subject is completely able to ignore the stimulus. This may be impossible in the waking, conscious subject. On the other hand, during natural sleep, subjects are said to be in a state of "unconsciousness". In this context, the term "unconsciousness" is used to describe an apparent lack of awareness of, or responsiveness to the external environment. Recording EPs during such a state may provide a means to dissociate exogenous from endogenous influences.

Stages of Sleep

Prior to sleep onset, the Waking period can be divided into Alert Wakefulness and Relaxed Wakefulness. Alert Wakefulness is comprised of relatively low voltage, mixed frequency EEG activity recorded when the subject is alert with their eyes open. Relaxed Wakefulness, recorded while the subjects' eyes are closed, occurs

immediately prior to sleep onset and is comprised mainly (>50%) of alpha (8-12 Hz) and low voltage, mixed frequency EEG activity.

Most sleep researchers classify sleep into a series of five stages, each of which is defined by unique EEG, EOG and EMG patterns which predominate in each consecutive 30 s epoch of recorded activity (Rechtschaffen and Kales, 1968). Stage 1 characterizes the transition period from wakefulness to sleep and is thus considered the sleep onset period. During this stage the EEG shows predominantly low voltage, mixed frequency (2-7 Hz) activity accompanied by slow rolling eye movements. Stage 2 is characterized by the onset of phasic sleep spindles (12-14 Hz) and large amplitude, negative-positive deflections known as a "K-Complexes". These two phasic events occur in a background of relatively low voltage, mixed frequency EEG activity. Stages 3 and 4 are collectively known as slow wave sleep and are differentiated by an increased proportion (moderate to large) of high amplitude, low frequency delta (0-2 Hz) activity. Stage 3 is comprised of between 20% and 50% of delta activity whereas stage 4 is comprised of more than 50% delta activity per epoch. The fifth sleep stage is characterized by periodic, rapid eye movements and has thus been labelled, REM sleep. Also characteristic of REM sleep is reduced muscle tonus recorded in conjunction with relatively low voltage, mixed frequency EEG activity. This lower amplitude, higher frequency EEG during REM is similar to that of Wakefulness and Stage 1 sleep.

ERPs in Sleep and Sleep Onset

Studies investigating the extent of information processing during sleep have commonly analysed differences between ERPs recorded during wakefulness and those recorded during sleep. The first study to investigate ERP activity during sleep was conducted by Davis et al. (1939), who observed EEG fluctuations which corresponded to the presentation of the auditory stimuli. The observable changes to the EEG record probably reflected K-Complex activity, a phasic phenomenon characteristic of non-REM sleep (Rechtschaffen and Kales, 1968), which occur spontaneously and which may also be elicited/evoked (Bastien and Campbell, 1992, 1994; Côté et al., 1996). Since the work of Davis et al., much research has focussed on ERPs and information processing during sleep.

Short-latency auditory evoked potentials (occurring between 0 and 12 ms post-stimulus) reflect the activity in auditory nerve and brain stem relay centres. As mentioned earlier, the BAEP response remains relatively unaltered during sleep (Amadeo and Shagass, 1973; Osterhammel et al., 1985; Campbell and Bartoli, 1986; Bastuji et al., 1988), regardless of stimulus intensity and/or rate of presentation (Campbell and Bartoli, 1986; Deacon-Elliot et al., 1987). Stelmack et al. (1993) did report a slow potential shift overlapping the BAEP during sleep but noted, however, that the changes were quite small. Thus, auditory processing at the periphery and brain stem relay centres would also likely appear unaltered during the transition from

wakefulness to sleep.

Findings concerning the mid-latency potentials (occurring between 12 and 50 ms post-stimulus) are more equivocal. Studies in which stimuli are presented relatively slowly sometimes show an attenuation during sleep while others show no differences (Amadeo and Shagass, 1973; Picton et al., 1974; Erwin and Buchwald, 1986). The only reliable sleep-related difference, has been found in studies which presented stimuli very rapidly (every 25 ms). Sleep causes an attenuation of the 40-Hz "steady-state" response (Linden et al., 1985; Jones and Baxter, 1988). The mid-latency response probably originates in the thalamus and the primary auditory cortex. Gating of information processing may therefore begin at this level of the nervous system.

The late components (occurring after 50 ms post-stimulus) are markedly altered by sleep. The P1 has been shown to either increase (Williams et al., 1962; Weitzman and Kremen, 1965), decrease (Osterhammel et al., 1985; Erwin and Buchwald, 1986), or show no change during sleep (Fursthorfer and Bergström, 1969; Weitzman and Kremen, 1965). During drowsiness P1 has been reported to decrease in amplitude (Aguirre and Broughton, 1987). Recently, Perrino and Campbell (1996) argued that the high-pass filter setting may account for some of the discrepant findings. When an inappropriately high setting is used, P1 may appear to decrease during sleep onset and sleep. However, when an appropriately long time constant is employed, P1 is consistently larger during sleep. Long time constants permit the recording of

overlapping and summating slow potentials. Little, however, is known about the functional significance of the P1 potential. This component is therefore usually analysed in relation to the N1 potential.

The N1 has consistently been shown to become attenuated during NREM sleep (Williams et al., 1962; Weitzman and Kremen, 1965; Fursthorfer and Bergström, 1969; Kevanishvili and von Specht, 1979; Paavilainen et al., 1987; Noldy et al., 1988; Nielsen-Bohlman et al., 1991; Campbell et al., 1992; Ogilvie et al., 1991, 1994; Salisbury et al., 1992; Winter et al., 1995; Loewy et al., 1996). This decrease in the amplitude of the N1 has been found regardless of stimulus intensity (Campbell et al., 1988), or interstimulus intervals of between 1 and 12 ms (Armitage et al., 1990). During REM sleep, N1 rebounds to approximately 50% of its waking amplitude (Campbell et al., 1992; Loewy et al., 1996). The latency of the N1 potential is either unaffected by sleep (Weitzman and Kremen, 1965) or only slightly delayed (Campbell et al., 1992). N1 was also reported to decrease in amplitude during the sleep onset period (Noldy et al., 1988; Ogilvie et al., 1991). Noldy et al. (1988) presented stimuli at a rate of 1.1/s requiring subjects to respond at the start and end of each train of 100 stimuli. Sleep onset was defined using the Rechtschaffen and Kales (1968) definition of Stage 2 sleep. The requirement of a behavioural response may, however, have inhibited sleep onset. Ogilvie et al. (1991) also required subjects to respond with a button press to infrequently occurring

stimuli (presented at a variable ISI of between 1 and 30 s, with a mean of 17.2 s), which remained on for a period of up to 5 s or until the subject responded, whichever occurred first. Only when subjects failed to respond to between one and four stimulus presentations were they considered to be asleep. The slow rate of stimulus presentation may, however, have permitted the inclusion of Stage 2 sleep into the ERP average. The continuous presentation of the tone (which remained on for 5 s or until the subject responded) may have altered the morphology of the ERP waveforms. The requirement that subjects respond to stimuli may also have prolonged the natural onset of sleep.

The effects of sleep on P2, like P1, is also quite variable. P2 may either increase (Kevanishvili and von Specht, 1979; Noldy et al., 1988; Campbell et al. 1992; Ogilvie et al., 1991, Harsh et al., 1994), decrease (Williams et al., 1962, 1964; Fruhstorfer and Bergström, 1969), or show little change in amplitude during sleep (Weitzman and Kremen, 1965). The equivocal results of the P1 and P2 changes during sleep is likely due to the different procedures used to record the data (Campbell et al., 1992). Again, when an appropriately long time constant is used and when baseline-to-peak measurement is used, P2 typically increases in amplitude during NREM sleep. During sleep it would, therefore, appear that both P1 and P2 increase in amplitude when N1 decreases to near baseline level. As mentioned previously, this is most easily explained by the removal of a long-lasting negativity that overlaps the P1-N1-P2 potentials. Campbell et al.

(1992) have labelled this the "wNd" wave. Employing a somewhat opposite interpretation, Näätänen and Picton (1987) suggested that sleep may result in the addition of a long-lasting positive wave. The effects of sleep on P2 latency is also equivocal. Some have found the latency to either increase (Kevanishvili and von Specht, 1979), decrease with approaching sleep (Fruhstorfer and Bergström, 1969), or to remain unchanged (Williams et al., 1962; Williams et al., 1964; Weitzman and Kremen, 1965).

A large amplitude negative ERP occurring at about 350 ms post-stimulus appears to be unique to sleep. For this reason, it is called the "sleep N2" to distinguish it from the N2 observed in waking studies (Näätänen and Picton, 1987). This sleep N2 is larger over the central region of the scalp and for this reason has also been called the "vertex sharp wave" (Campbell et al., 1992). This potential typically increases with the onset of sleep (Williams et al., 1962; Weitzman and Kremen, 1965; Ornitz et al., 1967; Noldy et al., 1988; Ogilvie et al., 1991; Harsh et al., 1994), although this may not always be the case. N2 may reflect the periodic incorporation of evoked K-Complexes into the ERP average (Weitzman and Kremen, 1965, Fruhstorfer, 1971; Campbell et al., 1992). The K-Complex contains negative and positive deflections peaking at approximately 550 ms (N550) and 900 ms (P900) respectively (Ujszászi and Halász, 1986; Bastien and Campbell, 1992, 1994; Campbell et al., 1992). A number of studies have also suggested that a negative wave (N350), which often precedes the K-Complex, may also contribute to this phasic

phenomenon (Ujszászi and Halász, 1986). Thus, inclusion of the K-Complex into the ERP average may contribute to an enhancement of the N2 wave.

More recently, studies have employed the auditory "oddball" paradigm to investigate the extent to which subjects are able to discriminate stimuli during sleep. Correct discriminations may be registered by either having subjects count the number of target stimuli or button-press whenever they detect the occurrence of a target stimulus. If subjects accurately detect the target stimuli, a late positive P3 wave will be recorded. P3 is maximum over parietal sites. In easy discrimination tasks, P3 peaks at approximately 300 ms, thus its alternative nomenclature, "P300". Little or no P3 activity is recorded if subjects either ignore or are fail to detect target presentation (see Donchin, 1981; Pritchard, 1981; Donchin and Coles, 1988; Picton and Hillyard, 1988; Picton, 1992). The P3 is thus a good measure of conscious awareness during sleep. Evidence for the occurrence of a P3 response during sleep, however, remains equivocal. While some studies have failed to confirm the existence of a P3 response (Paavilainen et al., 1987; Kutas, 1990; Campbell et al., 1992; Winter et al., 1995; Loewy et al., 1996), others *have* reported a P3 in sleep (Wesensten and Badia, 1988; Harsh et al., 1990; Hull et al., 1990; Nielsen-Bohlman et al., 1991; Salisbury et al., 1992). Paavilainen et al. (1987) found no significant differences between the amplitude of frequent vs. rare waveforms while subjects were asleep. They concluded that, while asleep, subjects

are unable to detect the differences in tones. Winter et al. (1995), and Nielsen-Bohlman et al. (1991) observed a late positive wave peaking at approximately 450 ms during Stage 2 sleep. The late positive wave had a central distribution, unlike the expected parietal maximum of a true P3. A possible explanation of the P450 wave is that the rare deviant stimuli may have elicited occasional large amplitude K-complexes. The K-complex consists of N350-P450-N550-P900 components. Since the rare stimuli will elicit the K-complex more often than the frequent, it would be expected that both N350 and P450 would be larger to the deviant stimuli. The P450 may be an artifact of the averaging of the N350-P450-N550-P900 components of the very large K-complex which would have occasionally been elicited by the deviant, target stimuli. This late positivity seen during sleep may, therefore, reflect partial activity arising from the K-Complex (Ujszászi and Halász, 1986; Campbell et al., 1992). Salisbury et al. (1992), recorded a P3 wave during Stage 2 sleep having similar latency and distribution to the P3 observed during wakefulness. They reported that sleep apparently attenuated the amplitude of the P3, and suggested, therefore, "... that the P3 contains a component which reflects the automatic, pre-attentive evaluation of deviant stimuli" (p. 256). Harsh et al. (1990), however, remarked that the P3 they recorded became delayed, and reaction times slowed, when subjects became drowsy. The P3 eventually disappeared when subjects stopped responding to the target stimuli during Stage 2 sleep. The distribution of the peak

P3 recorded in sleep is reportedly more anterior than that of the P3 recorded during wakefulness (Nielsen-Bohlman et al., 1991). In some studies reporting a P3 response during sleep, the peak amplitude is delayed by as much as 500 ms compared to the waking P3 (Wesensten and Badia, 1988; Nielsen-Bohlman et al., 1991).

Focus of this Thesis

The transition from wakefulness to definitive sleep has been labelled as the sleep onset (SO) period (Ogilvie and Wilkinson, 1984). This period provides a naturally occurring model with which to investigate changes in ERPs associated with the transition from a fully conscious (attentive) to an unconscious (inattentive) state. Investigation of changes which occur to the auditory ERP during the SO period should allow for the dissociation of endogenous attentional influences from the exogenous sensory influences believed to contribute to the N1 potential.

Focus of Experiment 1: Evoked potential studies of how the SO process affects the vertex potentials (P1-N1-P2) have not always shown consistent results. Previous investigations have traditionally employed slow rates of stimulus presentation with ISIs of 1 or more seconds (Noldy et al., 1988; Ogilvie et al., 1991; Harsh et al., 1994; Winter et al., 1995). It has been know for some time that it is exceeding difficult to ignore stimuli presented at slow rates (Hillyard et al., 1973; Schwent et al.,

1976a; Näätänen, 1990). In addition, some sleep studies have required behavioural responses (typically a button press upon detection of a "signal") from the subject (Noldy et al., 1988; Ogilvie et al., 1989; Harsh et al., 1994). The requirement of an overt response may in itself inhibit or delay sleep onset. The first study investigated changes to the vertex potential using speeded rates of stimulus presentation. No behavioural response was required.

Focus of Experiment 2: The second study investigated the effect that the rate of stimulus presentation had on the vertex potential during the SO period. A slower rate of stimulus presentation was employed. As in the first study, subjects were not required to make any behavioural response.

Focus of Experiment 3: One problem often encountered in research of SO is a limited description of the topographical distribution of the P1-N1-P2 evoked potentials. It remains unclear as to what topographical changes occur to the vertex potential during sleep onset. Scherg and Picton (1991) have indicated that the vertex N1 potential might reflect the activity of two bilateral source dipoles active at the time of the P1-N1-P2 potential. Giard et al. (1994) have also indicated additional frontal sources, perhaps reflecting non-specific, attention-triggering "consciousness". Giard et al. (1988; 1994) have indicated that the scalp topography of the N1 is different from

that of other attentional related negativities (ie. "Nd") which may overlap with it. N1 is maximal over the fronto-central areas of the scalp whereas the early Nd wave (occurring at about the same time as N1) is maximal centrally and the late Nd wave is maximal frontally (Giard et al., 1988). N1 inverts in polarity at the mastoid when a nose reference is used (Alho et al., 1986), whereas both the early and late Nd waves do not. In addition, when a monaural stimulus is used, N1 has a contralateralized distribution whereas the distribution of the early Nd wave is more symmetrical (Woods and Clayworth, 1987; Giard et al., 1988). An extensive scalp distribution study of the changes which occur at sleep onset has yet to be carried out. The purpose of the third study was, therefore, to compare topographical maps of the N1 and the different wNd waves. Voltage distribution spline and CSD maps were computed. Giard et al. (1988) have indicated that the CSD maps, unlike voltage distribution maps, can help localize cortical source activity. wNd activity was measured as the difference in ERPs between sleeping and waking conditions. If the maps are different, the intra-cranial sources must also be different. On the other hand, if the maps are not different, the intra-cranial sources cannot be considered to be different. In the third study, several novel methodological changes were made. Most importantly, subjects were required to make an overt button press upon detection of a rare, "target" stimulus. Evidence of conscious awareness could thus be supported by: (1) the frequency and amplitude characteristics of an "aroused" EEG; (2) the actual

behavioural detection of the target; (3) a large amplitude N1 to the frequently occurring stimuli; and (4) the presence of a P3 to the target stimulus.

Chapter 2

Experiment 1:

THE EFFECT OF SLEEP ONSET ON EVENT-RELATED POTENTIALS WITH RAPID RATES OF STIMULUS PRESENTATION

The purpose of the first study was to examine the changes that occur to the P1-N1-P2 "vertex" potential during the sleep onset period. Previous studies have indicated that N1 is attenuated to near baseline level during Stages 2, 3 and 4 of sleep while P1 and P2 may increase in amplitude. There is less consistency in the sleep onset literature, perhaps because of the variety of stimulus parameters and rates of presentation that have been employed. In Experiment 1, a number of methodological controls were implemented. Stimuli were presented unusually rapidly (every 600 ms). Stimuli that are presented rapidly are less intrusive than those presented slowly. To further reduce unwanted arousals from the sleep onset period, subjects were not required to make an overt response to the stimuli. This article has been formatted according to the journal *Electroencephalography and Clinical Neurophysiology*, to which it was submitted. It has since been published in this journal (1996, 98: 484-492).

Introduction

Sleep onset (SO) is associated with many changes to psychophysiological measures including the electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), and other polygraphic recordings including respiration, heart rate, and electrodermal activity. Changes in these measures are not, however, always consistent. For example, although most subjects manifest a slowing of the EEG as they become increasingly drowsy, some may show a slowing of EEG activity while remaining awake or faster frequencies while asleep (Johnson, 1973; Ogilvie & Wilkinson, 1984). Many authors have also, therefore, employed performance measures during the SO period (Ogilvie & Wilkinson, 1984; Noldy et al., 1988; Ogilvie et al., 1989; Harsh et al., 1994). Performance on tasks (usually measured by the accuracy of detection of external signals or a slowing of reaction time) gradually deteriorates with increasing sleepiness. Unfortunately, engaging subjects in a task may in itself inhibit or delay sleep. As an alternative or a complement to performance measures, some labs also record event-related potentials (ERPs) during the SO period (Noldy et al., 1988; Nielsen-Bohlman et al., 1991; Ogilvie et al., 1991; Campbell et al., 1992; Harsh et al., 1994).

A variety of sensory and cognitive evoked potentials have been recorded during actual sleep. The early latency exogenous potentials (typically those occurring within the first 12 ms following stimulus presentation) are unaltered (Amadeo & Shagass,

1973; Osterhammel et al., 1985; Campbell & Bartoli, 1986; Erwin & Buchwald, 1986; Deacon-Elliot et al., 1987; Bastuji et al., 1988) or show only relatively small changes during sleep (Stelmack et al., 1993).

Several longer latency ERPs (those occurring after 50 ms) are markedly influenced by sleep. The auditory P1-N1-P2 'vertex' complex is the most frequently studied. N1, peaking between 75 and 150 ms, is greatly attenuated during NREM sleep (Näätänen & Picton, 1987; Campbell et al., 1988; Nielsen-Bohlman et al., 1991; Bastuji et al., 1995). The reduction in the amplitude of N1 has been found regardless of stimulus intensity, ranging from 60 to 100 dB (Campbell et al., 1988), or the interstimulus interval (ISI), ranging from 1 to 12 seconds (Armitage et al., 1990). N1 (or subcomponents which overlap it in time and space) has also been found to vary with the subject's level of attention (Näätänen & Picton, 1987; Näätänen, 1990). At sleep onset, N1 gradually declines in amplitude (Noldy et al., 1988; Ogilvie et al., 1991; Bastuji et al., 1995), possibly due to a decrease in the subject's level of attention. The decrease in the amplitude of N1 is parallelled by a slowing of the behavioural reaction time (Noldy et al., 1988; Ogilvie et al., 1991).

The earlier P1, peaking at approximately 50 ms, and later P2, peaking at approximately 200 ms, have also been reported to be altered by sleep. There is, however, some controversy about the direction of this change. Some authors report a decrease in P1 amplitude (Osterhammel et al., 1985; Erwin & Buchwald, 1986),

while others report an increase (Campbell et al., 1992). P2 amplitude may increase during NREM sleep (Nielsen-Bohlman et al., 1991; Ogilvie et al., 1991; Campbell et al., 1992; Bastuji et al., 1995), but the change has not always been found consistently (Salisbury et al., 1992). Some of the contradictory findings may be due, in part, to the technique used to measure the ERP waveform. Some studies employed a peak-to-peak amplitude measure while others, a baseline-to-peak measure. Peak-to-peak amplitude will vary with change in either one or both of the peak deflections. It is also possible that if both peaks are overlapped by a long-lasting slow wave, the corresponding peak-to-peak measure might not change. This is because the removal of the summating effects of, for example a negative slow wave, will cause negative peaks to decrease but positive peaks to increase in amplitude. Baseline-to-peak measures can index amplitude change independently of the effects of overlapping slow waves.

There have also been reports that a late N2, peaking at approximately 350 ms, significantly increases in amplitude at sleep onset (Ornitz et al., 1967; Ogilvie et al., 1991; Harsh et al., 1994). Others, however, have not observed this trend (Noldy et al., 1988).

ERP studies at sleep onset have generally employed slow rates of stimulus presentation, with ISIs ranging from 1 to 30 s. It has been known for some time that it is exceedingly difficult to ignore stimuli that are presented slowly. For example, differences in the amplitude of P1-N1-P2 peak deflections due to

manipulation of the subject's level of attention, become much smaller as the rate of stimulus presentation is slowed (Schwent et al., 1976a; Näätänen, 1990). This may explain some of the inconsistencies in ERP results at sleep onset. Even when differences have been reported, they do not typically emerge until relatively late in the sleep onset period, perhaps because stimuli presented slowly intrude into conscious awareness, thus delaying sleep. Stimuli that are presented rapidly are much easier to ignore (Schwent et al., 1976a). For this reason, an unusually rapid rate of presentation was used in this study.

Method

Subjects

Eight (1 male, and 7 female) healthy, right-handed undergraduate university students volunteered to participate in this study. Subjects were between the ages of 21 and 32 (mean = 24.7 years, SD = 3.7 years). All were self-reported "good sleepers". None of the subjects reported a history of hearing or neurological disorders. They were instructed to refrain from alcohol and caffeine use within 24 hours of testing. Prior to testing, each subject signed a consent form. All subjects received a $20 honorarium for their participation in this study.

ERP Recording

The electroencephalogram (EEG) and electro-oculogram (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 (Fz, Cz, Pz, and Oz) and also from the right mastoid (RM) and the mid-point between the right mastoid and Fz (RFM). The EEG electrodes were referenced to the nose (Alho et al., 1986). A "true" vertex N1 (often referred to as "N1b") should invert in polarity at the mastoid when a nose reference is used. EOG activity was recorded between the supra- and infra-orbital ridges of the right and left eyes respectively. 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 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 kOhms. ERP data were collected using two linked IBM-compatible 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. Chart speed on the polygraph was set at 10 mm/s.

The EEG and EOG data were digitized using a 12-bit analogue-to-digital (A/D) converter. Digitization started 50 ms prior to

stimulus onset and continued for another 500 ms following it. A total of 256 data points were sampled per channel (i.e., one sample every 2.15 ms). Single trials were stored on disk for later, off-line analyses. In order to reduce high frequency residual noise, ERPs were later digitally filtered in the frequency domain using a zero-phase shift low pass filter set at 15 Hz.

Stimuli

Evoked potentials were elicited using "standard" 1000 Hz tone pips (60 dB/SPL; 50 ms duration; rise/fall time of 5 ms). Two different infrequently-occurring deviant stimuli had identical parameters to the standard tone except for a variation in their pitch (either 1100 or 2000 Hz). The auditory stimuli were synthesized using an InstEP Systems 16-bit waveform generator card. Stimulus probability was .80 for the standard stimuli and .10 for each of the two different deviant stimuli. Only the ERPs to the standard stimuli will be presented in this article. Stimuli were randomly presented with a fixed ISI of 600 ms, in blocks of 1000 trials. 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 subject in spite of possible changes in head or body position (Campbell & Bartoli, 1986). A Bruel and Kjaer 2209 sound level meter was used to calibrate the auditory signals.

Testing Procedure

Subjects were instructed to arrive at the laboratory approximately two hours before their normal bedtime during which time electrodes were affixed and baseline testing took place. Testing began during the waking state when subjects were asked to lie on their backs and to read a book (Alert Wakefulness condition). The EOG was monitored to ensure subjects continued to read. 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 during Stages 2 and, if time permitted, Stages 3 and 4 of sleep. In order to maximize the amount of data collected during the relatively short sleep onset period, each subject was awakened repeatedly, approximately once every hour. Five onset periods were obtained for each subject. In five cases, time permitted the collection of an additional sleep onset condition. To verify they were awake, subjects were asked a simple question. Once the subject was awakened and had correctly answered the simple question, they were then allowed to resume sleep at which point stimulus presentation was resumed. The ERP data were only stored for further analyses if the transition from wakefulness to sleep was captured within a block of trials.

Data Scoring and Analysis

Single trial data were rejected off-line if either the EEG or EOG amplitude exceeded +/- 100 μV during wakefulness or Stage 1 sleep. Unusually large amplitude eye movements (typically saccades while reading) or eye blinks would thus be rejected during the waking state. Large amplitude slow horizontal eye movements occurring during Stage 1 were also rejected although this was a relatively rare occurrence (fewer than 2% of trials). Single trial data in Stage 2, 3 or 4 sleep were rejected if either the EOG or EEG amplitude exceeded +/- 150 μV (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 (AW - the reading condition), Relaxed Wakefulness (RW - lights out with eyes closed), Stage 1 sleep (S1), Stage 2 sleep (S2), and Slow Wave Sleep (SWS - combined Stages 3 and 4 sleep). RW was defined by a predominance (>50%) of low voltage alpha EEG activity (8-12 Hz), and occasional rapid eye movements or blinking. S1 sleep was defined by relatively low voltage, mixed frequency EEG activity (2-7 Hz), and the presence of slow rolling eye movements (Rechtschaffen & Kales, 1968). Stages 2, 3 and 4 were also defined by the standard Rechtschaffen and Kales scoring criteria. Single trial ERPs were sorted and averaged within each

sleep/wake stage. Data were then collapsed across all sleep onset periods.

Only the midline electrode sites were statistically analyzed. ERPs from the lateral sites were at times difficult to discern in the background noise. Grand-average vertex waveforms were visually assessed to determine the peak latency range for each deflection. The P1-N1-P2 latency windows were: 45-115 ms, 80-175 ms, and 140-230 ms respectively. A late negative wave, N2, was measured between 300 and 400 ms. The average of the pre-stimulus interval served as a baseline from which peak deflections were measured. P1, N1, P2 and N2 maximum peak amplitudes were initially scored at Cz where ERPs tended to be largest. The latency of the Cz maximum peak deflection was used as the time point for amplitude measurement on the other channels. Completely within-design, two-way repeated measures ANOVAs (BMDP, 1988), were calculated for the peak amplitude of each deflection. The within factors were condition (AW, RW, S1, S2, and SWS) and electrode site (Fz, Cz, Pz, and Oz). Results were considered to be statistically significant at an alpha value of 0.95. Greenhouse-Geisser (1959) correction factors were used when applicable.

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 SO period to 87 s during the fifth SO period. There was, however, no general trend among the five replications toward a shorter SO time. Overall, the mean SO latency was 111 s. It should be noted that the relatively fast SO latencies were sometimes missed in the present experimental paradigm. Only when a full transition from wakefulness to Stage 2 sleep occurred were the data further analyzed. The mean number of averaged trials per subject within the AW, RW, S1, S2 and SWS stages were 1070, 1142, 653, 2611 and 1072 respectively.

The vertex ERPs in the different waking and sleeping conditions are superimposed in Figure 2.1. Peaks P1, N1, P2 and N2 are identified in the figure. Their latency tended to become prolonged as the subject became increasingly drowsy and finally entered definitive sleep (Stages 2 and SWS). P1, N1, P2 and N2 peaked at 62, 109, 180 and 313 ms respectively during AW and at 73, 121, 192 and 354 ms respectively during SWS. None of these changes was statistically significant.

-------- Insert Figure 2.1 about here --------

Waveforms from all electrode sites and for all individual subjects in the different waking and sleeping conditions are superimposed in Figure 2.2. It can be seen that the effects of sleep onset are, in general, consistent across subjects. The grand average waveforms for these subjects is shown in Figure 2.3. As can be seen in this figure, N1 tended to invert in

polarity at the mastoid. The mean amplitude values of P1, N1 and P2 for each of the midline electrode site are presented in Table 2.1.

------ Insert Figures 2.2 & 2.3 and Table 2.1 about here ------

There were no significant P1-N1 or N1-P2 peak-to-peak amplitude differences among sleep/wake stages. However, several significant baseline-to-peak differences were found. Of particular interest are the conditions in which significant differences first emerged. A significant electrode site by sleep stage interaction was observed for the amplitude of P1, $F(12,72) = 3.26$. Simple main effects testing indicated that P1 was significantly larger (i.e., more positive) during S1 sleep compared to RW at the Fz and Cz electrode sites. Differences at Pz only emerged when Stage 1 was compared to AW. No significant differences were found between AW and RW, or between S1 and S2 sleep at any scalp site.

A significant main effect was observed for the amplitude of N1, $F(4,24) = 10.00$. N1 was initially significantly attenuated during Stage 1 compared to RW. Again, no significant differences were found between AW and RW, or between S1 and S2 sleep. The condition x electrode site interaction was not significant.

A significant electrode site by sleep stage interaction was also found for P2 amplitude, $F(12,72) = 4.72$. Significant simple main effect testing revealed that at Fz and Cz, P2 was larger

(i.e., more positive) during S1 sleep than RW. At Pz, P2 differences only emerged when the subject entered SWS when it became significantly larger than during Stage 2, Stage 1, RW or AW. As was the case for P1 and N1, no significant differences were found between AW and RW, or between S1 and S2 sleep for any electrode site.

An a priori prediction toward an increase in the amplitude of N2 at SO was made. This was, however, not observed. If anything, N2 tended to decrease in amplitude with increasing sleepiness.

Five replications were required to provide a sufficient number of trials for averaging purposes. For this reason, it was not possible to statistically compare differences across replications. Figure 2.4 presents the grand averages for each of the five replications. As can be observed, there were no systematic changes across these replications.

-------- Insert Figure 2.4 about here --------

Discussion

The finding that the progression from Alert Wakefulness to Slow Wave Sleep is associated with a gradual and significant reduction in the amplitude of the N1 confirms previous findings (Noldy et al., 1988; Nielsen-Bohlman, 1991; Ogilvie et al., 1991). N1 tended to invert in polarity at the mastoid during the

waking and sleeping states. Thus, although N1 latency was prolonged during sleep onset, its scalp distribution suggests that the intra-cranial generators are similar in each condition.

In addition, a parallel increase in the amplitude of P1 and P2 was observed. Thus, when peak-to-peak amplitudes (P1-N1 and N1-P2) were measured, no significant differences emerged. It is, therefore, not N1 per se that is affected by sleep onset. Rather, it would appear that a slow negative wave that overlaps the P1-N1-P2 waking waveform is removed at sleep onset. Näätänen and Picton (1987) have interpreted sleeping data in an opposite manner; a slow *positive* wave is *added* to the sleeping waveform. Since there is no absolute zero in the EEG, whether changes during sleep and sleep onset reflect a slow positive wave being added to sleeping ERPs or a slow negative wave being removed from waking waveforms may be somewhat arbitrary. It is not, however, incidental. The essence of this argument appears to be centred on whether the subject is inhibiting processing during the sleep state or whether actively enhancing processing during the waking state. This controversy is similar to the one surrounding selective attention (see Näätänen, 1990) - is there additional processing of the attended channel (reflected by the addition of a negative slow wave) or inhibition of processing of the unattended channel (reflected by the addition of a positive slow wave).

In the awake subject, attention results in a negative slow wave that overlaps the N1-P2 peaks. The negative differences

between the attended and unattended channels has been labelled "Nd" (Hansen & Hillyard, 1980). This endogenous wave is apparently *added* to the exogenous wave (Hansen and Hillyard, 1980; Näätänen & Picton, 1987). Campbell et al. (1992) compared differences found when subjects are either asleep or awake to those when they are either attending or not attending stimuli. A long-lasting slow negative wave overlaps the vertex potential when subjects were awake (whether attending to, or ignoring the stimulus). The negative difference wave between sleeping and waking ERPs has been labelled "wNd" to distinguish it from the Nd observed in studies of selective attention (Campbell et al. 1992). Like "Nd", the most parsimonious explanation of wNd is a marked decrease in the ability to maintain attention between the alert-waking and the drowsy-sleeping states. Alternately, as already mentioned, it is also possible that a slow positive wave may be added to the ERP at sleep onset, perhaps reflecting inhibition of further information processing. Of course there are many physiological and biochemical changes that occur between the two states, any one of which might be used to explain wNd. An examination of the grand averages indicates that wNd begins before the peak of P1, at approximately 25-40 ms following stimulus presentation. In selective attention tasks, Woldorff et al. (1987) indicated that Nd can also begin this early when a channel to-be-attended is easily discriminated from one to-be-ignored.

In the present study, ERP differences tended to arise early

in the sleep onset period. Fluctuation in ERPs was initially observed during the relaxed wakefulness condition. This is probably because the subjects were not actively engaged in a task as was the case in other studies. Alternatively, monotony associated with the rapid rate of stimulus presentation (every 600 ms) might have prevented periodic arousals that occur when stimuli are presented at slower rates. Of course, since subjects were not required to actively detect the stimuli (since this, in itself, might disturb sleep onset), it is not possible to determine if the changes that were observed are a reflection of fluctuation in conscious awareness. Finally, the relaxed wakefulness period is probably not a uniform state. Subjects would be less aroused near the transition to Stage 1 than at the beginning of the recording session.

It is unlikely that inclusion of infrequently occurring deviant stimuli contributed to the finding of an ERP change early in the SO period. If anything, deviants should interfere with SO, resulting in a delay of the ERP following standard stimuli such that ERP changes should occur at a later time. We found no evidence of this.

Stage 2 is used by many laboratories as point of sleep onset (Johnson, 1973; Salisbury et al., 1992). Stage 1 is considered to be a transition between the waking and sleeping states (Ogilvie & Wilkinson, 1984; Ogilvie et al., 1991). This is because most subjects can make behavioural responses to external stimuli (presented at slow rates) during Stage 1 sleep. Furthermore, the

present study points out another problem when using Stage 1 as the definition of SO. The amplitude of ERPs may be markedly altered during Stage 1 (when stimuli are presented rapidly) or may be only slightly altered during Stage 1 (when stimuli are presented slowly). Thus, even though the characteristics of the EEG remain constant during Stage 1, the extent of information processing may be quite different. Subjects may or may not make overt responses during Stage 1. The ERPs may or may not be altered.

Näätänen (1990) has suggested that N1 may act as a transient-detector system that triggers an internal attentional system. N1 may subserve "conscious perception of auditory stimuli in general", and furthermore, "without indicating what the stimulus is or what its precise features are" (p.212). In the present study, the peak of N1 was at or near pre-stimulus baseline level during Stage 1 sleep. Although the baseline-to-peak amplitude of P1, N1 and P2 were much affected during Stage 1, the P1-N1 and N1-P2 peak-to-peak measurements were not. Näätänen and Alho (1995) pointed out that there is much confusion between what is termed "task-independent" and "task-dependent" processing. During Stage 1 sleep, attention-related (task-dependent) processes cease early (at the time of P1), terminating the overlapping negativity. However, this does not terminate the processing of the physical characteristics of the stimulus (task-independent). Presumably, the physical characteristics of the stimulus are fully elaborated. In this regard, short-latency

exogenous evoked potentials reflecting the extraction of physical characteristics of the stimulus are also relatively unaffected by sleep (Bastuji et al., 1988).

There is thus at least some evidence that loss of consciousness occurs at about this time. "Consciousness" in this context is defined by an absence of awareness of the external stimulus. Of course, since neither independent self-report nor behavioural measures of conscious detection were employed in this study, such an interpretation must be heeded with caution. The results are nevertheless consistent with studies that have concomitantly recorded ERPs and measures of performance (Noldy et al., 1988; Ogilvie et al., 1989, 1991; Harsh et al., 1994). The gradual decrement in N1 amplitude has also been observed during anaesthetic-induced loss of consciousness (Plourde & Picton, 1991; van Hooff et al., 1995).

N2 did not increase in amplitude at sleep onset as others have observed (Ornitz et al., 1967; Ogilvie et al., 1991; Harsh et al., 1994). Rather, if anything, it tended to decrease in amplitude. In the Ogilvie et al. (1991) study, stimuli were presented with a random ISI of 1 to 30s. When the inter-stimulus interval is longer than 5 s, a vertex sharp wave (Picton & Hillyard, 1974) or a K-Complex may be evoked in Stage 2 of sleep. The number of K-Complexes that are evoked increases as the ISI is lengthened (Bastien & Campbell, 1994). Part of the K-Complex is a N350 wave. The inclusion of at least some K-Complexes in the ongoing sleep onset averages may have produced an apparent

enhancement of N2.

The present study indicated that significant ERP differences can be found as the subject enters Stage 1 of sleep. There are a number of problems in using ERPs in the applied, clinical setting. The amplitude of the ERP is very small relative to the background EEG observed at sleep onset. A large number of trials need to be presented in order to obtain a satisfactory signal-to-noise ratio. In many cases, the transition from the waking to the sleeping state occurred within a few trials. For this reason, *five* replications of the sleep onset procedure were required to obtain a sufficient number of trials to permit averaging. It was not possible to carry out a statistical analysis of ERP variation within each of the five replications because of the poor signal-to-noise ratio in some individual subjects. Nevertheless, an examination of the grand averages did not reveal systematic changes across replications.

Signal averaging techniques will limit the practical utility of ERPs as measures of sleep onset. Recent single trial methods (Childers et al., 1987; Möcks et al., 1988; Woestenburg et al., 1992) have been used to overcome this restriction. Some compromise may however be necessary. Single trial detection methods are best suited to applications in which the ERP is relatively large compared to the background noise. In the present study, it was quite small because of the fast rate of stimulus presentation. Slower rates of stimulus presentation will enhance the amplitude of the vertex potential (Näätänen & Picton, 1987)

but as mentioned, may inhibit sleep onset.

		AW	RW	S1	S2	SWS
P1	Fz	0.19 (.13)	0.34 (.17)	1.41 (.34)	1.50 (.31)	2.60 (.56)
	Cz	0.28 (.11)	0.58 (.23)	1.60 (.30)	1.65 (.31)	3.21 (.65)
	Pz	-0.06 (.17)	0.33 (.31)	0.93 (.28)	0.71 (.27)	2.1 (.42)
	Oz	-0.15 (.22)	-0.09 (.34)	0.21 (.25)	-0.18 (.27)	1.07 (.36)
N1	Fz	-1.99 (.60)	-1.56 (.57)	-0.53 (.45)	0.04 (.31)	1.77 (.61)
	Cz	-2.88 (.83)	-2.00 (.59)	-0.59 (.43)	-0.01 (.31)	1.79 (.67)
	Pz	-1.88 (.64)	-1.18 (.47)	0.03 (.30)	0.30 (.29)	1.57 (.34)
	Oz	-0.98 (.63)	-0.35 (.68)	0.29 (.16)	0.21 (.29)	1.11 (.41)
P2	Fz	-0.30 (.70)	0.70 (.43)	2.46 (.74)	2.73 (.49)	4.01 (.73)
	Cz	1.08 (.20)	1.96 (.27)	3.40 (.72)	3.39 (.53)	4.99 (.67)
	Pz	1.01 (.36)	1.83 (.34)	2.01 (.46)	1.99 (.38)	4.07 (.47)
	Oz	0.96 (.53)	1.61 (.48)	1.29 (.51)	0.81 (.40)	2.41 (.62)

TABLE 2.1. Mean amplitude (in μV) and standard error (in parentheses) for each ERP deflection (P1, N1, P2) for the midline electrode sites (Fz, Cz, Pz, Oz), during each stage of the wake/sleep cycle (Alert Wakefulness, Relaxed Wakefulness, Stage 1, Stage 2, Slow Wave Sleep).

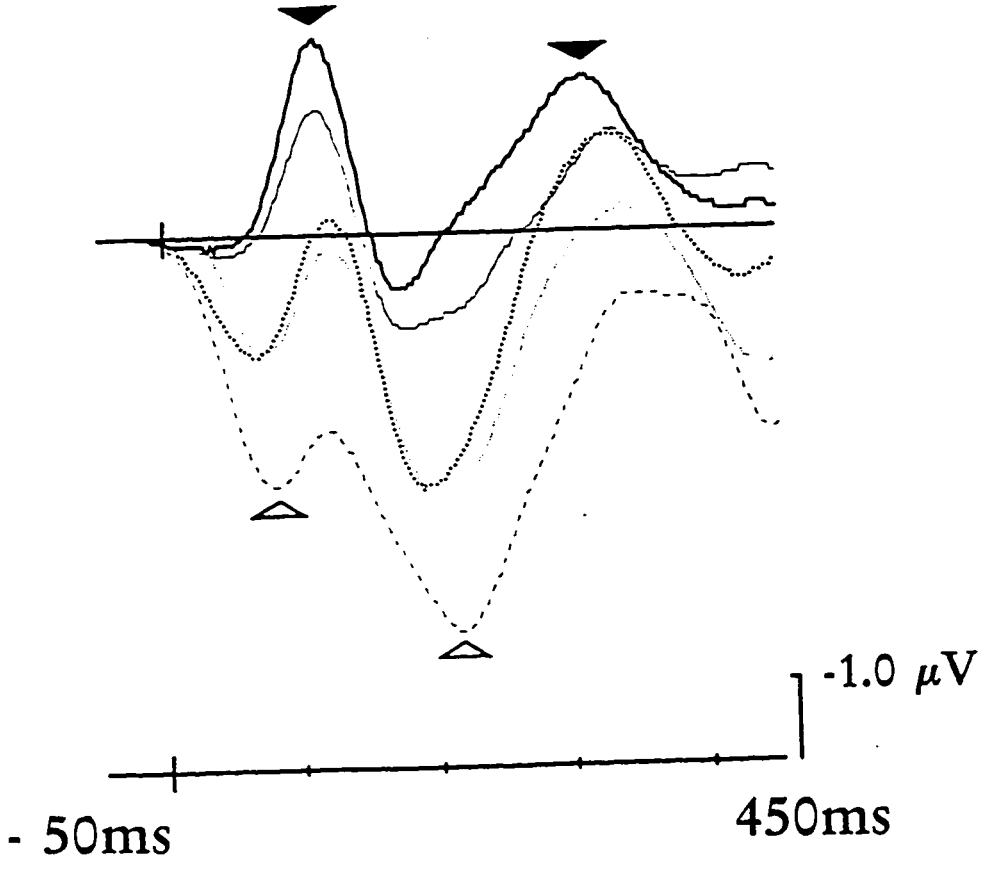
FIGURE LEGEND

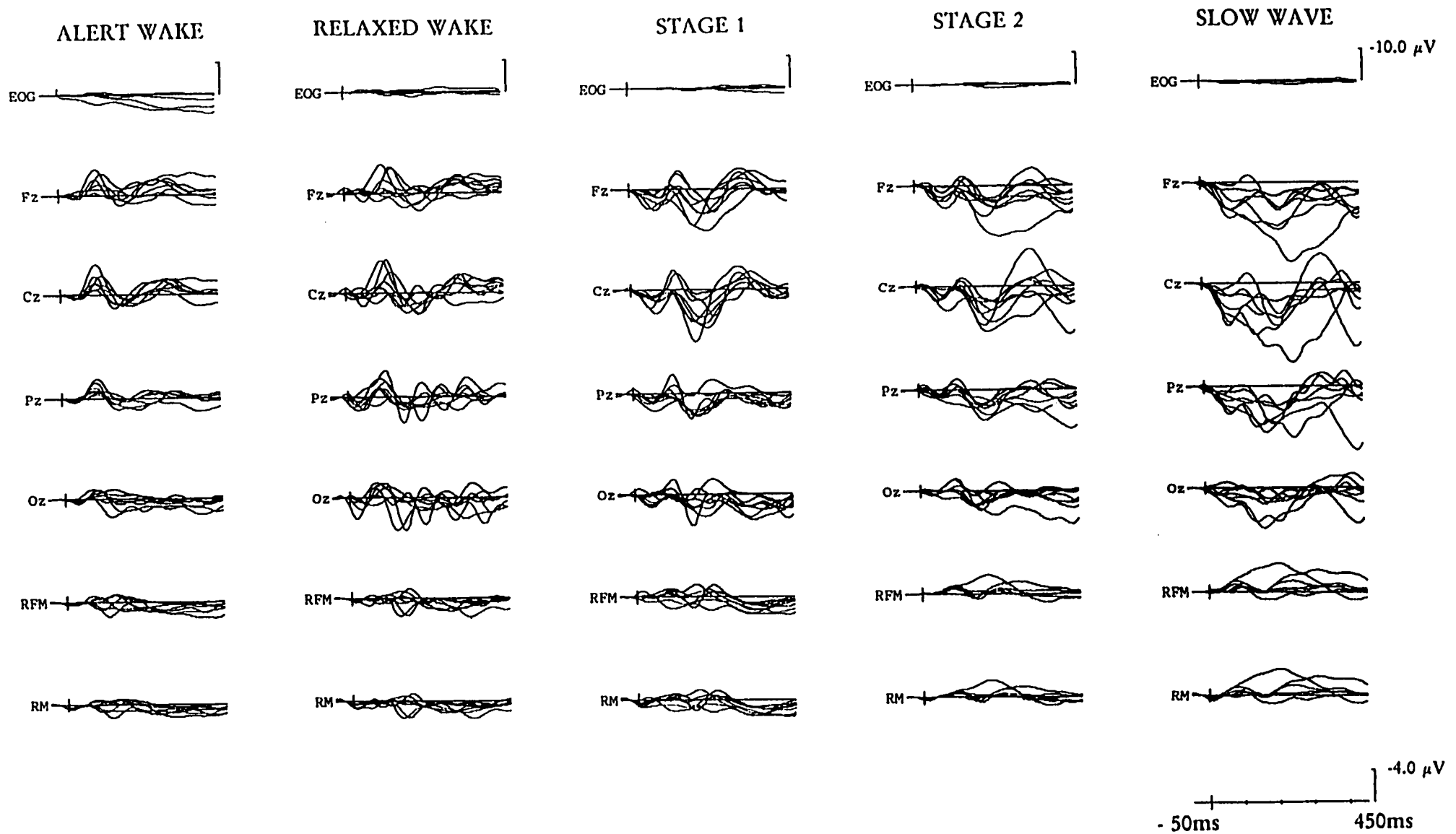
Figure 2.1. Superimposed vertex waveforms for each of the different wake and sleep conditions. N1 and N2 peaks are indicated by closed triangles, and P1 and P2 peaks are indicated by open triangles. A small increase in the latency of P1, N1 and P2 can be observed during sleep. All three deflections manifest marked amplitude changes during Stage 1 of sleep.

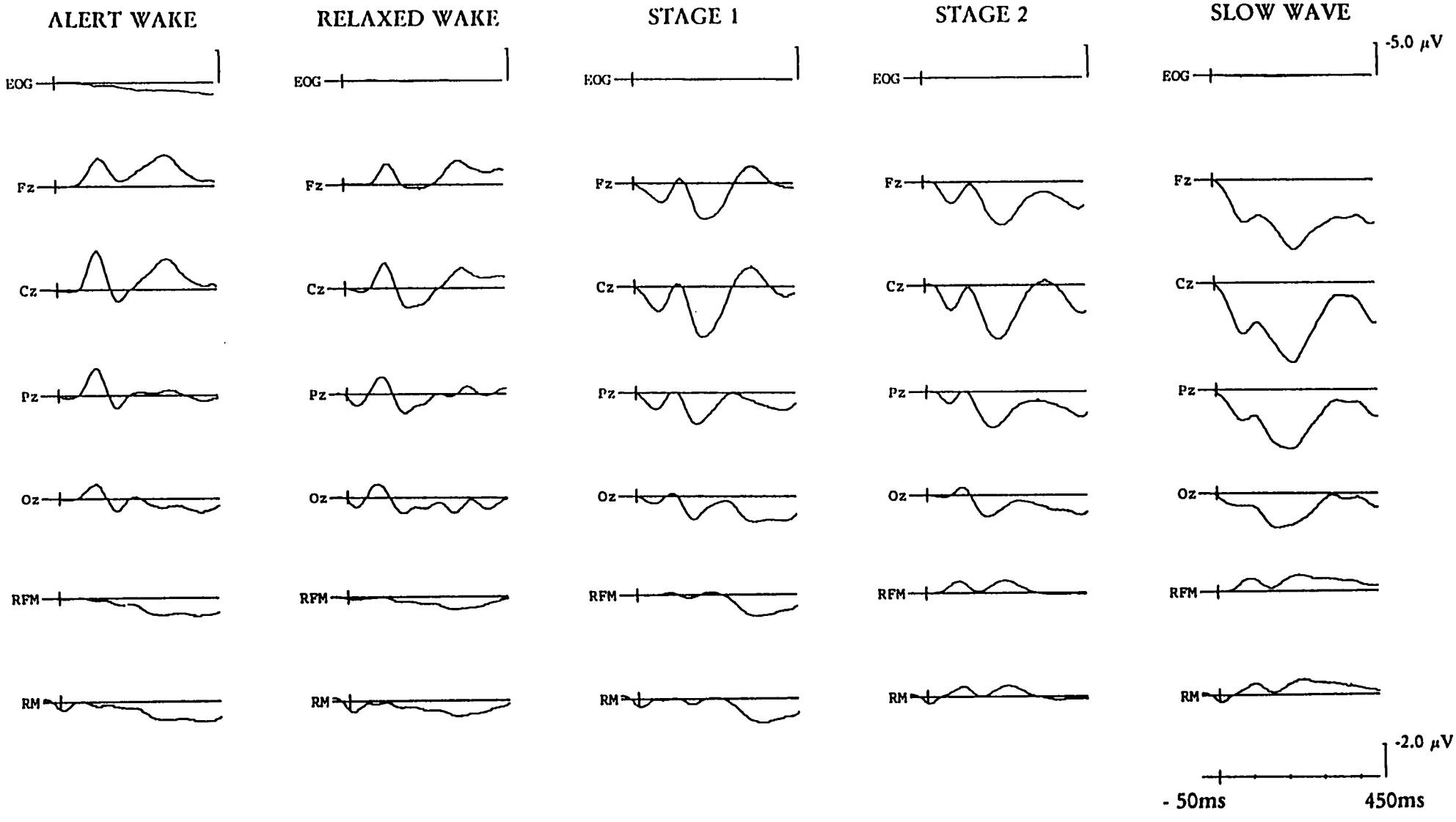
Figure 2.2. Superimposed waveforms for 8 individual subjects in each of the five wake/sleep states. In general, the transition from Alert Wakefulness to Slow Wave Sleep is consistent across subjects.

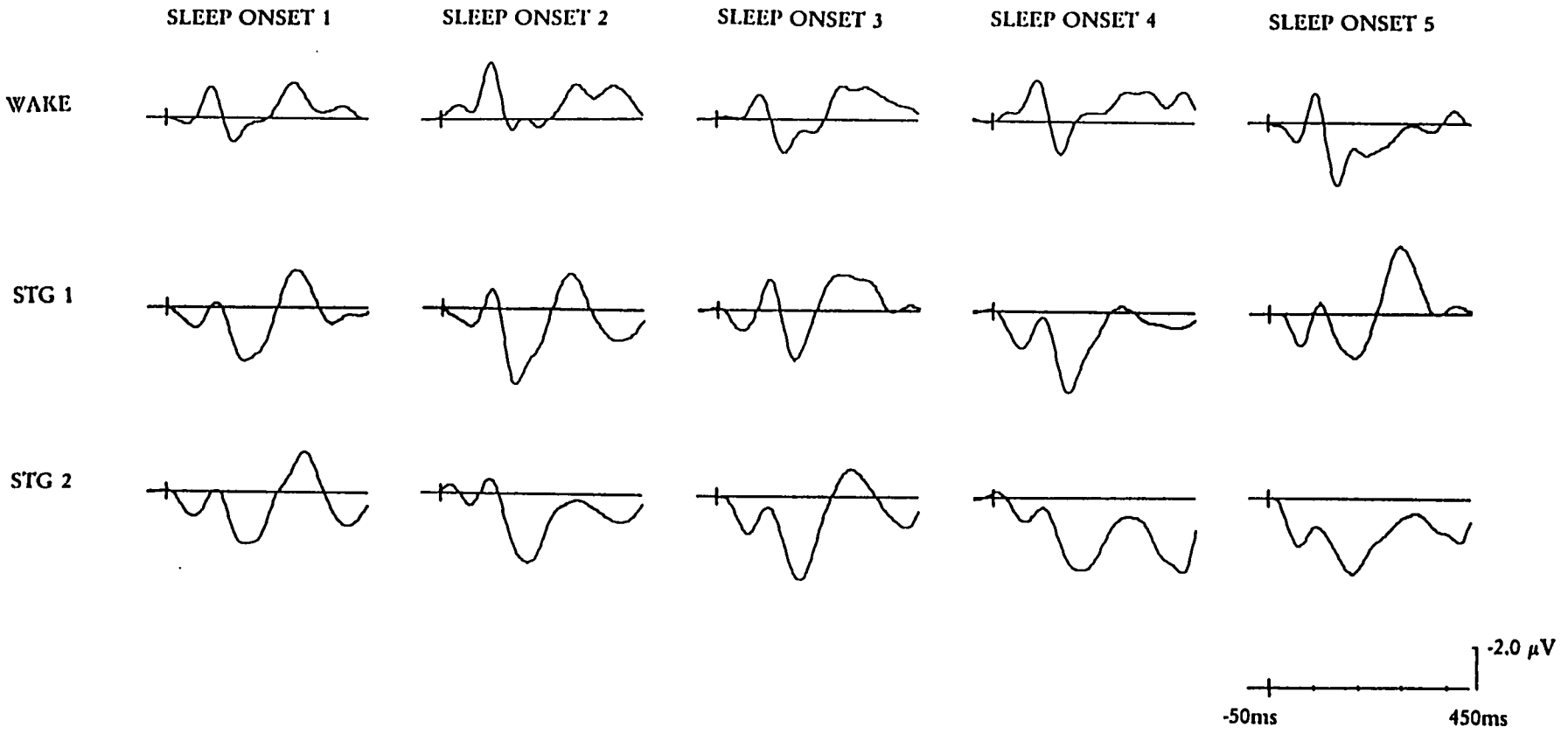
Figure 2.3. Grand average waveforms of individual subjects in Figure 2.2. The amplitude of N1 was reduced while that for P1 and P2 was augmented during Stages 1, 2 and Slow Wave Sleep.

Figure 2.4. Grand averaged vertex waveforms for the Relaxed Wakefulness, Stage 1 and Stage 2 sleep stages for each sleep onset period. There are no systematic changes across replications.


-1.0 μV
- 50ms
450ms
ALERT WAKEFULNESS
RELAXED WAKEFULNESS
STAGE 1
STAGE 2
SLOW WAVE


ALERT WAKE
RELAXED WAKE
STAGE 1
STAGE 2
SLOW WAVE
-10.0 μV
EOG
Fz
Cz
Pz
Oz
RFM
RM
-4.0 μV
- 50ms
450ms


ALERT WAKE
RELAXED WAKE
STAGE 1
STAGE 2
SLOW WAVE
-5.0 μV
EOG
Fz
Cz
Pz
Oz
RFM
RM
-2.0 μV
- 50ms
450ms


SLEEP ONSET 1
SLEEP ONSET 2
SLEEP ONSET 3
SLEEP ONSET 4
SLEEP ONSET 5
WAKE
STG 1
STG 2
-2.0 μV
-50ms
450ms

Chapter 3

Experiment 2:

AUDITORY EVOKED POTENTIALS AT SLEEP ONSET USING A SLOW RATE OF STIMULUS PRESENTATION

The results of the first experiment indicated that a long-lasting negative wave that overlaps P1, N1 and P2 is near baseline level during Stage 1 of sleep. Most other studies indicate that N1 is either unaltered during Stage 1 or somewhat attenuated. These studies differ from Experiment 1 in that they use slower rates of presentation and often require the subject to make an overt response. In Experiment 2 the rate of stimulus presentation was therefore slowed. However, subjects were again not required to make an overt response. This chapter follows the format of the journal *International Journal of Psychophysiology*. This article was submitted in December 1996.

Introduction

A series of late auditory "vertex" evoked potentials are much altered by sleep (Campbell et al., 1992). A negative deflection, "N1", maximum over fronto-central areas of the scalp peaking between 75 and 150 ms, is greatly attenuated during NREM sleep while earlier P1 and later P2 waves may increase in amplitude (Campbell et al., 1988, 1992; Nielsen-Bohlman et al., 1991; Bastuji et al., 1995; Winter et al., 1995). Recently, de Lugt et al. (1996) have indicated that this very marked change in the vertex potential begins to occur as early as the transition from the waking state to Stage 1 of sleep. This is in contrast to a series of other studies (Noldy et al., 1988; Ogilvie et al., 1991; Bastuji et al., 1995), who indicated that the vertex potentials shows a gradual change in amplitude during the sleep onset period. De Lugt et al. employed a short 600 msec. inter-stimulus interval (ISI) compared to the longer 1 to 2 sec. ISI employed in other studies (although it has been as long as 30 sec. -- Ogilvie et al., 1991). The studies also differed in that de Lugt et al. removed the requirement of an overt response to the stimuli. Stimuli presented at slow rates and/or those that require an overt response may interfere with the sleep onset process. The purpose of the present study is to determine if the gradual change in the vertex potential can be replicated when a longer ISI is employed, but when the requirement for an overt response is removed.

A second purpose of the present study is to examine the effects of sleep onset on a late negative wave, "N2", peaking at approximately 350 msec. Studies with relatively long ISIs suggest it increases in amplitude during the sleep onset process (Ogilvie et al., 1991; Harsh et al., 1994), while the de Lugt et al. (1996) study, using a shorter ISI, failed to find this difference. Some authors (see Picton et al., 1974; Näätänen and Picton, 1987) suggest that the late N2 may be related to a unique sleep phenomenon, the vertex sharp wave. A variety of late negative waves can also be elicited in waking subjects. In particular, an "N2b" appears to increase in amplitude to intrusive stimuli when waking subjects are engaged in a secondary task (Giard et al., 1994). This N2, however, inverts in polarity at the mastoid when a nose reference is used. The present study will, therefore, also employ a nose reference in an attempt to distinguish between the N2 observed in the waking and sleeping states.

Method

Subjects

Eight (5 male and 3 female) undergraduate students at the University of Amsterdam between the ages of 19 and 31 were paid to participate. All were medically healthy, self-reported "good sleepers" with no reported hearing difficulty or neurological

disorder. Subjects were instructed to refrain from caffeine, "soft" drug and alcohol consumption within 24 hours of testing. One subject was later rejected because of an inability to sleep.

ERP Recording

The electroencephalogram (EEG) and electro-oculogram (EOG) were recorded using silver-silver chloride electrodes. The EEG was recorded from the midline frontal, central, parietal, occipital and right mastoid scalp sites (Fz, Cz, Pz, Oz and M2). The reference was the tip of the nose. Horizontal and vertical EOGs were recorded using electrodes placed on the outer canthi of each eye and the supra- and infra-orbital ridges of the right eye, respectively. A ground electrode was placed on the forehead. Inter-electrode impedances were kept below 5 kOhms. The low-pass filter was set at 35 Hz. The time constant was 1 s. EEG and EOG were continuously digitized at 256 Hz using a 12-bit analogue-to-digital (A/D) converter and stored on hard disk for subsequent off-line analyses. Higher frequency noise was later digitally filtered in the frequency domain using a zero-phase shift low pass filter set at 15 Hz.

Stimuli

Evoked potentials were elicited using 80 dB SPL 1000 Hz tone pips having a total duration of 55 ms and a rise/fall time of 5 ms. Auditory stimuli were synthesized using an InstEP Systems 16-bit waveform generator card and presented binaurally through

earphone inserts. Stimuli were presented with a fixed ISI of 1000 ms in blocks of 400 trials.

Testing Procedure

Testing began during the waking state when subjects ignored the stimuli and read a book. This was verified by the presence of saccades in the horizontal EOG channel. This condition was repeated a second time to ensure the replication of results. The lights were then turned off and the subjects were allowed to fall asleep during which time a complete block of 400 trials was presented. In order to maximize the amount of data collected during the relatively short sleep onset period, each subject was awakened repeatedly, approximately every 30 minutes. Five onset periods were obtained for each subject. The ERP data were only stored for further analyses if the transition from wakefulness to sleep was captured within a block of trials.

Data Scoring and Analysis

The different stages of wakefulness and sleep were classified by two experienced scorers according to the criteria of Rechtschaffen and Kales (1968). In cases of stage ambiguity, the epoch was excluded from further analysis. Discrete epochs ("trials") were constructed from the continuous signal during off-line analyses. Each sweep started 53 ms prior to stimulus onset and continued for another 502 ms following it. During wakefulness, trials in which either the EOG or EEG exceeded +/-

100 μV were rejected from the average. During Stage 1 and Stage 2, this rejection level was increased to +/- 150 μV permitting most delta activity to pass. A 20 s sliding window epoch (10 s pre- and post-stimulus) was used for staging purposes. Single trial ERPs were sorted into four different sleep/wake stages: Alert Wakefulness (AW - the awake, reading condition), Relaxed Wakefulness (RW - lights out with eyes closed), Stage 1 sleep (S1) and Stage 2 sleep (S2). RW was defined by a predominance (>50%) of low voltage alpha EEG activity (8-12 Hz), and occasional rapid eye movements or blinking. S1 and S2 sleep stages were scored according to the criteria of Rechtschaffen and Kales (1968). Single trial ERPs were sorted and averaged within each sleep/wake stage. Data were then collapsed across all sleep onset periods.

Grand-average vertex waveforms were visually assessed to determine the peak latency range for each deflection. The P1, N1, P2 and N2 latency windows were: 45-90 ms, 65-150 ms, 160-260 ms and 300-400 ms respectively. The average of the pre-stimulus interval served as a baseline from which peak deflections were measured. P1, N1, P2 and N2 maximum peak amplitudes were initially scored at Cz where ERPs tended to be largest. The latency of the Cz maximum peak deflection was used as the time point for amplitude measurement on the other channels. Completely within-design, two-way repeated measures ANOVAs (BMDP, 1988), were calculated for the peak amplitude of each deflection. The within factors were condition (AW, RW, S1 and S2) and electrode

site (Fz, Cz, Pz, and Oz). Results were considered to be statistically significant at an alpha value of 0.95. Greenhouse-Geisser (1959) correction factors were used when applicable.

Results

Grand average waveforms for each electrode site and for each wake/sleep condition are shown in Figure 3.1. Peaks P1, N1, P2 and N2 are identified in this Figure. Mean amplitude and standard error values for each ERP deflection at each site and for each wake/sleep stage are presented in Table 3.1.

------ Insert Figure 3.1 and Table 3.1 about here ------

P1 peaked at 57 ms during Alert Wakefulness. Neither its latency nor amplitude showed significant differences during the sleep onset period although its amplitude did increase in Stage 2 sleep. N1 peaked at 103 ms during Alert Wakefulness. It was maximum over fronto-central areas of the scalp and inverted in polarity at the mastoid. During Stages 1 and 2 of sleep, N1 also appeared to be inverted at the mastoid although this was more difficult to observe as it tended to decrease to near baseline levels during definitive sleep (Stage 2). A significant main effect was observed for the amplitude of N1, $F(3,21)=8.18$. N1 was significantly attenuated during Stage 2 sleep compared to Alert Wakefulness, Relaxed Wakefulness and Stage 1 sleep. P2 peaked at

184 ms and was more centrally distributed. Its peak latency tended to become prolonged, and its amplitude larger, as subjects became increasingly drowsy (Stage 1) and finally entered definitive sleep (Stage 2). None of these changes were statistically significant.

There were no significant P1-N1 or N1-P2 peak-to-peak amplitude differences among wake/sleep stages. Grand averaged vertex waveforms for the four different wake/sleep stages are superimposed in Figure 3.2.

----- Insert Figure 3.2 about here -----

A late negative wave, N2, peaked at about 313 ms during Alert Wakefulness and at about 356 ms during Stage 2 sleep although this difference did not reach significance. N2 peaked at -1.20 μV during Alert Wakefulness. A clear N2 was not visible during Relaxed Wakefulness. N2 increased in amplitude in Stages 1 and 2 of sleep but the difference compared to the alert waking state was not significant. N2 inverted in polarity at the mastoid during Alert Wakefulness. Although a small inversion was visible in Stages 1 and 2 of sleep, the inversion occurred later than the peak of N2 recorded over frontal and central sites. In Relaxed Wakefulness a late positive wave was observed at central and posterior sites.

Discussion

In the present study, a gradual change in the amplitude of the P1-N1-P2 vertex potential was observed during the transition from the waking state to Stage 1 of sleep. This is in contrast to the results observed by de Lugt et al. (1996) who noted a very large change during Stage 1 sleep. These results are, however, very similar to those reported by Noldy et al. (1988), and Ogilvie et al. (1991) who also used slower rates of stimulus presentation. These studies also required subjects to actively signal the detection of the stimuli. An overt, behavioural response was not required in the present study. The shift to a gradual change in the vertex potential as opposed to the rapid change observed by de Lugt et al. (1996), therefore appears to be due to the effects of stimuli that are presented slowly. Schwent et al. (1976a), indicated that essentially identical rates of stimulus presentation can have remarkably similar effects on the amplitude of N1 in subjects when the level of selective attention is manipulated. It would appear that stimuli presented at slow rates are difficult to ignore. In the context of sleep onset, such slowly presented stimuli may "intrude" into consciousness, thus delaying definitive sleep. Of course, in the absence of independent behavioural evidence, such an interpretation must remain tentative.

There were no P1-N1 or N1-P2 peak-to-peak differences. As

outlined in the de Lugt et al. (1996) study, the gradual increase in the positive peaks, P1 and P2, and the gradual decrease in the negative peak, N1, can be explained by the removal of a slow negative wave that overlaps the waking P1-N1-P2 components[1]. The slow waking negative wave is similar to the Nd wave described by Näätänen (1990) who noted that heightened attention results in the addition of a negative slow wave to the P1-N1-P2 complex. Campbell et al. (1992), labelled the negative slow wave that overlaps the waking ERP "wNd" to distinguish it from the Nd observed in studies of selective attention. The removal of the slow negative wave during the sleep onset period may reflect a gradual loss of conscious awareness of the auditory stimulus. This transition from a conscious to an unconscious state (from wakefulness to sleep) can occur relatively early in the SO process (de Lugt et al., 1996), or later as found in the present study. Thus, the point at which sleep onset occurs appears to depend upon the extent of "intrusion" from the external environment.

---

[1]Näätänen and Picton (1987) have suggested that during sleep a slow positive wave is *added* to the waking waveform with the result that P1 and P2 increase while N1 decreases in amplitude. The issue of whether a slow negative wave is removed from the waking waveform or whether a slow positive wave is added to the sleeping waveform is beyond the intent of this article. The debate is similar to that used for the effects of selective attention. Attended channels may receive additional processing (as reflected by an additional slow negativity). For a more complete discussion of this issue, the reader is referred to Näätänen and the rebuttal to his model (Näätänen, 1990).

The increase in the amplitude of N2 during Stage 2 sleep, while not significant, was similar to findings in previous reports (Ogilvie et al., 1991; Harsh et al., 1994). There is some question as to whether the waking and sleeping N2s, occurring between 300 and 400 ms, reflect the same process. Giard et al. (1994), described a waking N2 (which they labelled "N2b") that can be elicited by intrusive stimuli in alert yet inattentive subjects. This N2 inverts in polarity at the mastoid. The N2 wave that was recorded in our alert and awake subjects showed a similar inversion in polarity at the mastoid. The N2 observed in Stages 1 and 2 did not show the same extent of inversion nor was its temporal resolution similar. It would therefore appear that the waking and sleeping N2s reflect different intra-cranial processes. The sleep N2 could be a manifestation of a vertex sharp wave (Picton et al., 1974) or alternatively may be related to the N350 component of the K-Complex (Bastien and Campbell, 1992; Harsh et al., 1994; Winter et al., 1995). Interestingly, when subjects were awake but passive (during the relaxed waking state), a relatively large positive wave appeared over posterior sites. Its scalp distribution and latency are similar to that of a P300. This positive wave might be a reflection of an intrusion of the stimulus into consciousness. On the other hand, the amplitude of P300 is inversely proportional to the probability of stimulus occurrence (Duncan-Johnson and Donchin, 1977; Campbell et al., 1992). P300 should, therefore, have been difficult to observe with the single train of invariant stimuli used in this

study. Again, independent behavioural evidence is required to resolve this issue.

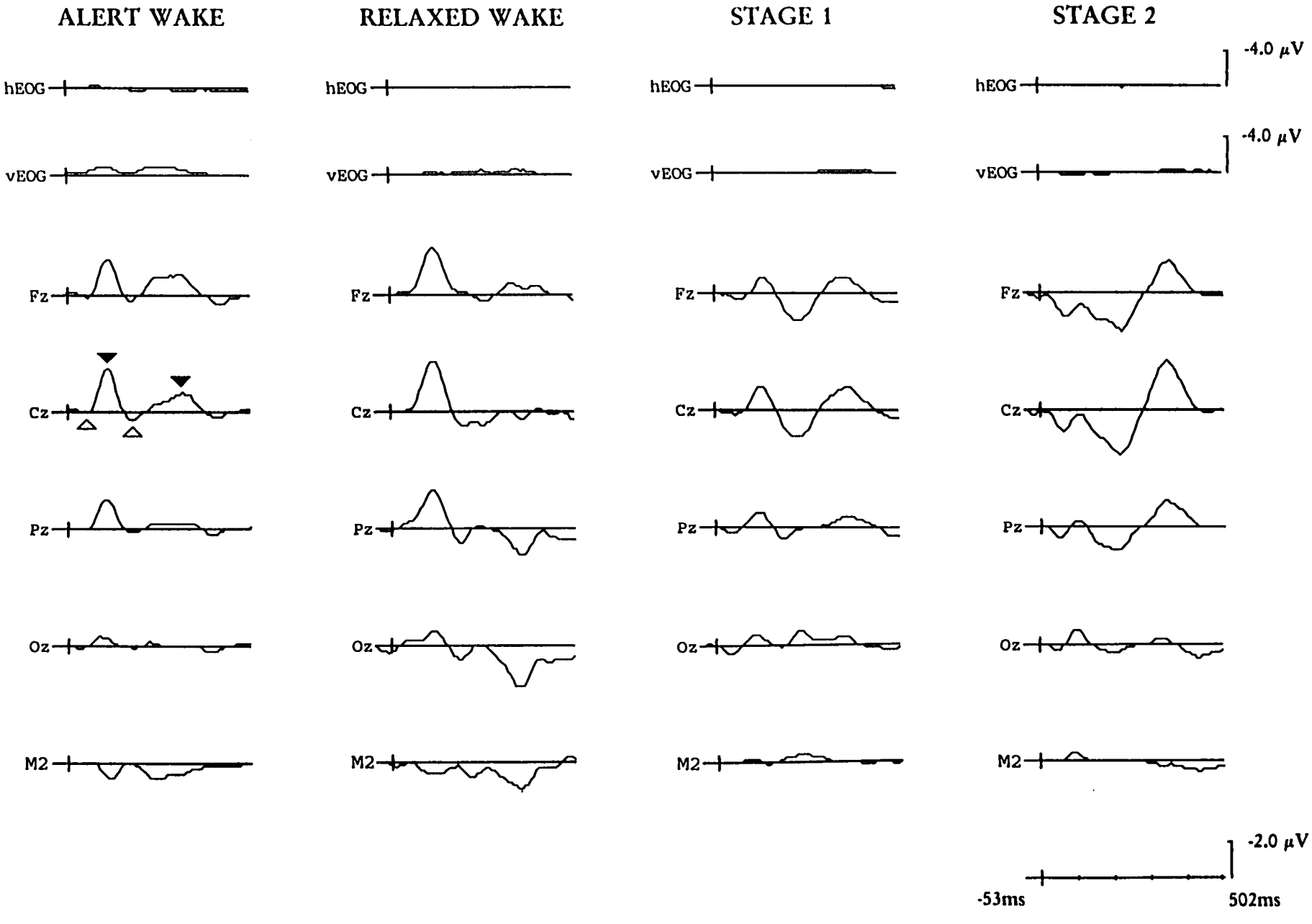
		Alert Wakefulness	Relaxed Wakefulness	Stage 1 Sleep	Stage 2 Sleep
P1	Fz	0.10 (0.31)	0.36 (0.44)	0.76 (0.19)	1.41 (0.22)
	Cz	0.30 (0.29)	0.35 (0.47)	0.53 (0.23)	1.33 (0.20)
	Pz	0.35 (0.24)	0.03 (0.39)	0.15 (0.25)	0.54 (0.15)
	Oz	-0.05 (0.20)	0.13 (0.23)	-0.90 (0.35)	0.09 (0.09)
	M	0.17 (0.10)	-0.16 (0.47)	-0.31 (0.18)	-0.23 (0.13)
N1	Fz	-2.33 (0.62)	-3.19 (0.87)	-1.40 (0.30)	0.19 (0.18)
	Cz	-2.23 (0.66)	-3.15 (0.82)	-1.79 (0.39)	0.09 (0.24)
	Pz	-1.23 (0.58)	-2.06 (0.71)	-0.93 (0.28)	-0.20 (0.37)
	Oz	-0.69 (0.58)	-1.36 (0.58)	-0.75 (0.29)	-0.43 (0.35)
	M	0.97 (0.30)	0.54 (0.47)	0.06 (0.23)	-0.09 (0.16)
P2	Fz	0.48 (0.25)	1.44 (0.90)	2.08 (0.52)	2.18 (0.39)
	Cz	1.08 (0.27)	1.72 (0.84)	2.13 (0.54)	2.55 (0.53)
	Pz	0.79 (0.33)	0.53 (0.21)	0.70 (0.36)	1.31 (0.38)
	Oz	0.54 (0.32)	0.46 (0.29)	-0.13 (0.47)	0.74 (0.29)
	M	0.70 (0.36)	0.36 (0.36)	-0.39 (0.28)	0.14 (0.20)
N2	Fz	-1.26 (0.37)	-2.10 (0.82)	-1.89 (0.54)	-1.93 (0.55)
	Cz	-1.20 (0.37)	-1.59 (0.79)	-2.51 (0.39)	-2.95 (0.82)
	Pz	-0.68 (0.33)	-0.68 (0.82)	-0.99 (0.24)	-1.56 (0.49)
	Oz	-0.31 (0.31)	0.25 (0.61)	-0.20 (0.32)	-0.36 (0.30)
	M	0.56 (0.27)	0.89 (0.43)	0.19 (0.17)	0.43 (0.14)

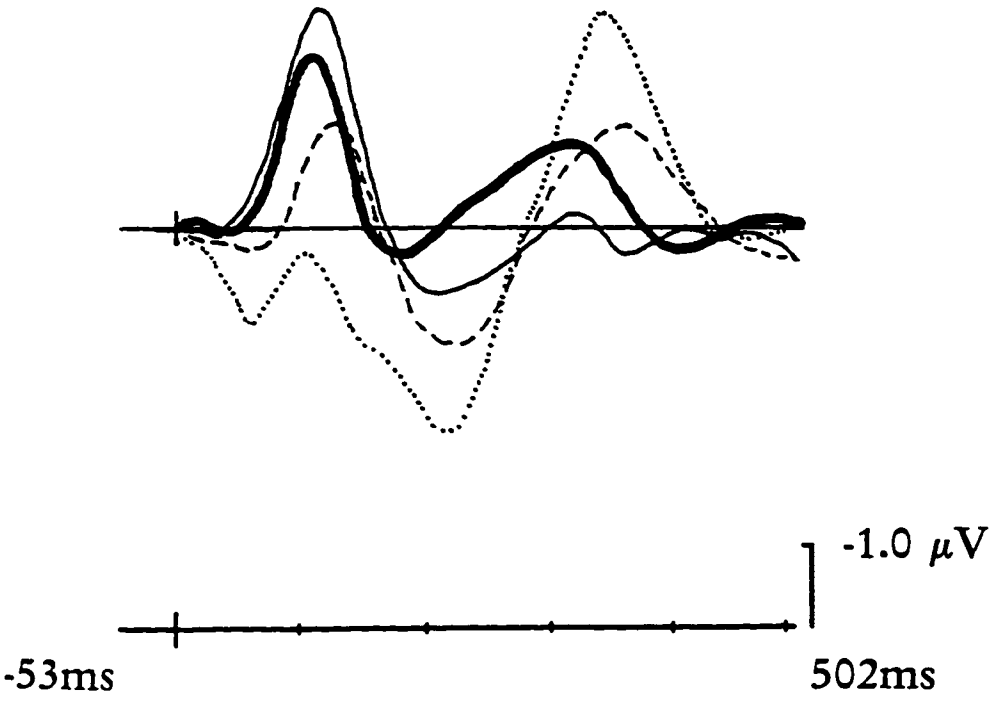
Table 3.1. Mean amplitude (in μV) and standard error (in parentheses) for each ERP deflection (P1, N1, P2, N2). Data are provided for each of the midline electrode sites (Fz, Cz, Pz, Oz) and the right mastoid (M2) during each stage of the wake/sleep cycle (Alert Wakefulness, Relaxed Wakefulness, Stage 1, Stage 2).

FIGURE LEGEND

Figure 3.1. Grand average waveforms for each electrode site and for each of the four sleep/wake states. The N1 and N2 peaks are indicated by closed triangles, and P1 and P2 peaks by open triangles. The amplitude of N1 was reduced while that for P1 and P2 was augmented during Stage 2 sleep.

Figure 3.2. Superimposed grand-averaged vertex waveforms for each of the different wake and sleep conditions. A small non-significant increase in the latency of P1, N1 and P2 can be observed during sleep onset. The N1 deflection manifests a marked amplitude change during Stage 2 of sleep.


ALERT WAKE
RELAXED WAKE
STAGE 1
STAGE 2
hEOG
vEOG
Fz
Cz
Pz
Oz
M2
-4.0 μV
-4.0 μV
-2.0 μV
-53ms
502ms



ALERT WAKEFULNESS
RELAXED WAKEFULNESS
STAGE 1
STAGE 2

Chapter 4

Experiment 3:

VOLTAGE AND CURRENT SOURCE DENSITY MAPPING OF CHANGES IN THE HUMAN AUDITORY EVENT-RELATED POTENTIAL DURING SLEEP ONSET

In Experiments 1 and 2, N1 was at baseline level during definitive sleep (Stage 2). Its amplitude during the waking state may therefore be due entirely to endogenous processes. The first two studies were unable to provide experimental evidence of the independence of the supposedly exogenous N1 and endogenous Nd. A second line of evidence to support the independence of N1 and Nd in the waking state is that their voltage distribution maps across the scalp are different. The purpose of the third study was, therefore, to map the N1 in the waking state and compare it to the wNd. The EEG was therefore recorded from 29 different scalp electrodes. In this study, stimuli were again presented slowly. However, subjects were asked to make an overt detection of an infrequently presented target stimulus. Consciousness could thus be defined according to (a) the actual behavioural response pattern, (b) the frequency characteristics of the EEG, (c) the presence of the late positive wave, P3, following the target and, as in the previous studies (d) the amplitude of the N1.

Introduction

The first two experiments of this thesis described the effects of sleep onset on late auditory evoked potentials. N1 gradually or rapidly decreased in amplitude (depending on the rate of stimulus presentation) while the amplitude of the positive waves P1 and P2 increased. The decrease in negativity and increase in positivity was explained by the removal of a long-lasting and summating negative slow wave, wNd, that overlapped the waking ERP. This wNd may be quite similar to the Nd reported in studies of selective attention.

In studies of selective attention, the additional processing negativity (PN) that the attended channel receives relative to the unattended can be observed as a negative difference (Nd) wave (Hansen and Hillyard, 1980). The Nd wave is computed by subtracting the ERP obtained while subjects ignored a channel from that obtained while they attended it. This endogenous Nd wave reflects the additional processing that the attended channel receives. This additional processing, like the wNd seen in studies of sleep onset, is added to, and overlaps the P1-N1-P2 components of the auditory ERP in the alert and awake subject (Näätänen and Picton, 1987).

Initial reports of the Nd wave have described both an early and a late attentional subcomponent (Hansen and Hillyard, 1980; Näätänen et al., 1981; 1982). Giard et al. (1988), however, also reported an additional, still earlier small amplitude Nd wave

(less than 1 μV) peaking at about 80 ms post-stimulus which was described as frequency specific. It was not, however, found in all conditions within their study and has not been reported elsewhere.

The second Nd component described by Giard et al. (1988) was a larger amplitude wave (about -3.0 μV) peaking between 100 to 200 ms post-stimulus depending on the ease of rejection of the unattended channel. This component is similar to the "early" Nd wave described by Hansen and Hillyard (1980) and Näätänen et al. (1981, 1982). This early Nd wave had a more central distribution, slightly posterior to that of the N1 potential and has, therefore, been described as the vertex component of the processing negativity (Näätänen et al., 1982), or as the central Nd wave (Hansen and Hillyard, 1984). Giard et al. (1988) suggested that both the N1 and the early Nd waveforms are independent and are probably "...due to summation of the activity of at least two brain generators separately located in the auditory areas of the two hemispheres" (p.381).

The "late" Nd, first described by Hansen and Hillyard (1980), was a small amplitude wave (about 2 μV) recorded maximally from the frontal electrode sites which peaked at about 340 ms post-stimulus. This late Nd wave has also been observed by Näätänen et al. (1981; 1982), and Giard et al. (1988). Current source density (CSD) analysis of the late Nd wave, however, showed no frontal components (Giard et al., 1988). CSD maps are better able to reflect brain generators located near the scalp

surface as they are more sensitive to the depth of source activity than are spline potential (SP) maps (Perrin et al., 1987; Picton et al., 1995). Giard et al., therefore, interpreted the difference in the frontal distribution of the late Nd wave between spline and CSD maps as reflecting source activity located deeper within the brain.

A possible interpretation for the decrease of N1 to near baseline level during sleep is that it is completely endogenous in nature, depending entirely on the attentional-conscious state of the subject. Such an interpretation would be in sharp contrast to that postulated by Näätänen (1990) and Hansen and Hillyard (1980). They theorized that N1 is an exogenous waveform dependent on the physical characteristics of the stimulus. The apparent endogenous, attentional influences on N1 were explained by the overlapping influence of the Nd slow wave.

Näätänen (1990) concluded that the true N1 is exogenous in nature, depending only on the physical characteristics of the stimulus. Nd, on the other hand, is endogenous, depending on the additional processing that the attended stimulus receives. This, exogenous-endogenous dichotomy relies on the assumption that the two processes do not interact. Justification for the independence of N1 and Nd comes from two lines of evidence: (1) experimental manipulations affect each component independently, and (2) the scalp distributions of each component.

The experimental evidence comes from the fact that Nd can be dissociated independently from N1. It is not only N1 that is

affected by manipulation of the subject's level of attention. Indeed the peak of Nd may overlap with the N1 peak when the channel to be attended is quite different from that to be ignored, or it may be much later than the peak of N1 when the attended and ignore channels are quite similar (Näätänen, 1990). N1 remains large in the to-be-ignored channel because of the constant physical attributes of the stimulus. When the attend and ignore channels are quite similar the subject must continue to process information until well after the peak of N1. As already mentioned, during sleep, when subjects are most able to inhibit information processing (i.e., to ignore stimuli), N1 is at or near baseline level.

A second line of reasoning adopted by those favouring the independence of N1 and Nd is that their scalp topographies are different. Giard et al. (1988) claim that the major difference between the distribution of N1 and the early Nd wave comes from a polarity inversion at the temporal electrode sites of the N1 data for both spline potential (SP) and current source density (CSD) maps. This polarity inversion was not observed for the early Nd wave. Moreover, N1 was found to have a contra-lateral dominance when stimuli were presented monaurally, unlike the early Nd wave.

These conclusions supporting the independence of N1 and Nd are based on evidence from studies employing selective attention tasks. This thesis maintains that these conclusions are flawed - it can also be argued that N1 is larger because subjects remain at least partially attentive to the ignored channel. In actual

fact there is considerable evidence of overlap between exogenous and endogenous processes during studies of attention. During the ignore condition, subjects remain at least partially aware of the eliciting stimuli. Thus, independence of N1 and the early Nd wave cannot be fully assessed until the effects of attention are completely removed from the waking, alert individual. This is typically accomplished in sleep onset studies. As mentioned throughout this thesis, sleep is the period of time during which subjects are least consciously aware of their external environment.

The hypothesis that the decrease in N1 to near baseline level during sleep onset is reflective of the loss of conscious awareness is, of course, dependent on the method used to measure "consciousness". In the first two studies, the subject's level of consciousness was determined by the frequency and amplitude characteristics of the EEG/EOG. Independent behavioural criteria, such as requiring subjects to signal their detection of the external stimulus, were not employed. A number of authors have now indicated that subjects are capable of consciously detecting external stimuli at least during Stage 1 sleep (Ogilvie and Wilkinson, 1984; Noldy et al., 1986; Ogilvie et al., 1989; Harsh et al., 1994). In Stage 2 sleep, behavioural responses are quite rare.

Another long-latency ERP significantly modulated by consciousness and attention is a late positive wave peaking at approximately 300 ms post-stimulus known as "P300" or "P3". P3 is

most often recorded during the so-called "oddball" task. A subject is asked to attend to a series of regularly occurring "standard" stimuli. Upon detection of an odd or rare target stimulus, P3 is elicited (Sutton et al., 1965; Donchin, 1981). P3 is maximum over parietal regions of the scalp. Although the precise functional role of P3 remains disputed (see Pritchard, 1981; Verleger, 1988; Donchin and Coles, 1988; Picton, 1992; Johnson, 1995), there is general agreement that it does involve some sort of conscious memory comparison process. If the subject fails to detect the target (i.e., to signal conscious awareness) or if they ignore the stimuli, P3 is not elicited (Hillyard et al., 1973; Squires et al., 1975b; Donald and Little; 1981). Furthermore, P3 is highly dependent on the probability of occurrence of the stimulus. As the probability of the target tone decreases, the amplitude of the P3 wave increases (Duncan-Johnson and Donchin, 1977; Campbell et al., 1979). Thus, the frequently occurring standard stimulus will elicit only a small P3. The late P3 positivity is difficult to observe during sleep (Wesensten and Badia, 1988; Bastuji et al., 1990; Campbell et al., 1992; Winter et al., 1995), a time when subjects are considered unconscious of, and inattentive to their surroundings.

The presence of P3 in the ERP waveform can, therefore, serve as an index that the subject made a conscious detection. The absence of a P3 must, however, be interpreted with caution. Subjects can consciously respond to the frequently occurring standard stimulus, yet do not show a P3. It is also possible that

subjects are conscious (in the sense of being awake and alert) but are ignoring the evoking stimuli and thus do not show a P3 even to the rare, target stimulus. The presence of a P3 is, therefore, evidence of conscious awareness. A failure to observe P3 is not, however, evidence of unconsciousness.

The purpose of this third study is to again compare the extent of exogenous and endogenous influences on N1. If N1 is entirely influenced by the exogenous, physical parameters of the stimulus, a gradual loss of consciousness should have little effect on its morphology. On the other hand, if it is entirely endogenous, removal of the overlapping wNd wave, should markedly affect the N1. Because of the ambiguity associated with the term "consciousness", three different independent measures will be employed:

1. The traditional frequency/amplitude characteristics of the EEG. This provides a measure of consciousness in the sense of "arousal" or "alertness".

2. The behavioural detection of a target stimulus by the subject. This provides a measure of what might be considered to be conscious "awareness". The failure to respond is, however, equivocal.

3. The amplitude of P3 following the target. Like the subject's behavioural response, this provides another measure of what might be considered to be conscious "awareness". However, the presence of P3 can be used as evidence of conscious awareness in the absence of a behavioural response.

Sleep onset studies have employed only a small number of electrodes, thus limiting spatio-topographic resolution. A topographical comparison of N1 and wNd, which is critical to determining their independence, could not be made. In the present study, the EEG will be recorded from 29 electrode sites. This enhancement of spatial resolution will allow for the computation of spline and current source density maps. If N1 and wNd have different intra-cranial generators, their scalp maps should be different.

Method

Subjects

Ten (4 male, and 6 female) healthy university students volunteered to participate in this study. The data from one female subject was excluded from subsequent analysis because of an excessively noisy EEG record. The remaining nine subjects were between the ages of 18 and 32 (mean = 23.7 years, SD = 5.8 years). All were self-reported "good sleepers". None of the

subjects reported a history of hearing or neurological disorders. They were instructed to refrain from alcohol and caffeine consumption within 24 hours of testing. Prior to testing, each subject signed a consent form. All subjects received a $25 honorarium for their participation.

ERP Recording

The electroencephalogram (EEG) and electro-oculogram (EOG) were recorded from tin electrodes. The EEG electrodes were affixed using the Electro-cap system of electrode placement (Blom and Anneveldt, 1982). Data were recorded from twenty-nine scalp locations according to the modified international 10-20 system of electrode placement (Picton et al., 1995). Electrodes were attached to the prefrontal (Fp1, Fp2), frontal (F9, F7, F3, Fz, F4, F8, F10), fronto-central (FC3, FC4), central (C3, Cz, C4), centro-parietal (CP3, CP4), parietal (P9, P7, P3, Pz, P4, P8, P10), temporal (T7, T8) and occipital (O1, O2) sites. Recordings from the left and right mastoids (M1, M2) were also measured (see Figure 4.1). The nose was used as a reference for all EEG channels. A "true" N1b response should invert in polarity at the mastoid when a nose reference is used (Alho et al., 1986; Giard et al., 1988). Horizontal and vertical EOG activity were recorded between the outer canthi of the left and right eyes, and supra- and infra-orbital ridges of the right eye respectively. A ground electrode was placed on the forehead. Inter-electrode impedances were kept below 5 kOhms. The physiological signals were amplified

with a time constant of 2 seconds and a 30 Hz low-pass filter. The EEG and EOG data were digitized using a 12-bit analogue-to-digital (A/D) converter. Data were continuously digitized at 128 Hz (i.e. one sample every 7.8 ms) and were stored on disk for later, off-line analysis.

------- Insert Figure 4.1 about here -------

Stimuli

Evoked potentials were elicited using "standard" 1000 Hz tone pips (70 dB SPL; 50 ms duration; rise/fall time of 5 ms) and infrequently-occurring "target" 1500 Hz tone pips which had otherwise identical parameters to the standard tones. Stimuli were synthesized using an InstEP Systems 16-bit waveform generator card. Stimulus probability was 0.96 for the standards and 0.04 for the targets. Stimuli were presented with a fixed interstimulus interval (ISI) of 1500 ms in blocks of 600 trials. Targets were presented pseudo-randomly such that there was a minimum of 30 s and a maximum of 45 s between presentations. Stimuli were presented binaurally via insert earphones. This system assured constancy of auditory input in the subject in spite of possible changes in head or body position (Campbell & Bartoli, 1986).

Testing Procedure

Subjects were instructed to arrive at the laboratory approximately two hours before their normal bedtime during which time electrodes were affixed and baseline testing took place. A small cylindrical response device was placed in the palm of their dominant hand and held in place by a comfortable elastic-cloth bandage. The response button was in close proximity to their thumb. A practice session was run to ensure that subjects understood the procedure. Subjects were asked to lie on their backs, relax with their eyes closed and to respond with a button press whenever they heard the target tone. The subject's reaction time (RT) was measured with a precision of 1 ms. Detection rates were greater than 0.98 for all subjects. Upon completion of the practice condition, the lights were turned off and subjects were permitted to fall asleep. Stimuli were presented throughout the sleep onset period and continued into Stage 2 of sleep until the 600 trials were presented. If subjects entered slow wave sleep (Stages 3 and 4) they were awakened and the data were stored for later offline analysis. In order to maximize the amount of data collected during the relatively short sleep onset period, each subject was awakened repeatedly, approximately once every half hour. To verify they were awake, subjects were asked a simple mathematical question. They were then permitted to fall asleep again during which time stimulus presentation resumed. Between ten and fifteen onset periods were obtained for each subject. Therefore, a total of between 6000 and 9000 stimuli were

presented to each subject.

Data Scoring and Analysis

The continuous EEG was divided into 30 s epochs for purposes of sleep scoring. These epochs were then classified by two experienced sleep scorers according to the criteria of Rechtschaffen and Kales (1968). Data were scored as either Wakefulness (W), Stage 1 sleep (S1) or Stage 2 sleep (S2). In cases of stage ambiguity, the epoch was excluded from further analysis. Inter-scorer agreement was about 90%. Wakefulness was defined by a predominance (>50%) of low voltage alpha EEG activity (8-12 Hz). Stage 1 sleep was defined by relatively low voltage, mixed frequency EEG activity (2-7 Hz), and the presence of slow rolling eye movements (Rechtschaffen & Kales, 1968). Stage 2 was defined by the occurrence of sleep spindles and/or K-complexes.

Evoked potential data were later reconstructed into discrete 1 s "single trial" standard and target epochs beginning 100 ms prior to stimulus onset and continuing for another 900 ms post-stimulus. Single trial data were rejected off-line if either the EEG or EOG amplitude exceeded +/- 100 μV. Unusually large amplitude eye movements or eye blinks would thus be rejected during the waking state. Large amplitude slow horizontal eye movements occurring during Stage 1 were, therefore, also rejected although this was a relatively rare occurrence (fewer than 2% of trials). Single trial epochs were then sorted and averaged

according to electrode site, stimulus type (standard/target) and wake/sleep stage. The data were then collapsed across all sleep onset periods. Target stimuli were also sorted and averaged according to whether subjects detected or missed the target. The average of the pre-stimulus interval served as a baseline from which peak deflections were measured. In order to reduce high frequency residual noise, the ERPs were subsequently digitally filtered in the frequency domain using a zero-phase shift low pass filter set at 15 Hz.

Statistical Analyses

Completely within-design, two-way repeated measure ANOVAs (Statistica, 1995), were calculated separately for the peak amplitude of each deflection elicited by the standard stimuli (P1, N1b, P2, N2). The within factors were condition (W, S1 and S2) and site (Fz, Cz and Pz). To reduce the possibility of chance findings, only the midline frontal, central and parietal EEG data were submitted for statistical analysis. Separate ANOVAs were also run for N1c (measured at T7 and T8) elicited by the standard stimuli, and P3 (measured at Pz) elicited by the target stimuli. A within-design, one-way repeated measure ANOVA was calculated for the latency value for each component measured at: Cz for P1, N1b, P2, and N2; T7 for N1c; and Pz for P3. Significant interactions and main effects were further analysed using Tukey's Honestly Significant Difference post-hoc test (Tukey, 1949).

Standard Stimuli: Grand-average vertex waveforms were visually assessed to determine the peak latency range for each deflection. P1, N1b, P2, and N2 were initially measured at Cz where ERPs tended to be the largest. The latency windows were: 40-100, 70-150, 100-250, and 200-400 ms respectively. Peak latencies at Cz were used as the time-point for amplitude measurement at the other electrode sites. N1c was measured at T7, as the maximum negative peak following the vertex N1b until 175 ms post-stimulus.

Target Stimuli: A late positive peak, P3, was measured at Pz following detected and non-detected targets. In Wakefulness and Stage 1 sleep, P3 was measured at Pz as the maximum positive peak occurring between 300 and 500 ms post-stimulus. In Stage 2 sleep peak detection for the missed targets was difficult. P3 was, therefore, measured as the average of all data points between 300 and 500 ms following stimulus onset. The relatively few missed target stimuli in Wakefulness and detected stimuli in Stage 2 sleep made peak identification difficult. These data were, therefore, not scored.

Performance and Reaction Time

Subjects' behavioural performance was recorded as either correct (hits) or incorrect (misses) in response to the presentation of each target stimulus. Subjects' accuracy and

reaction time (RT) data were then tabulated across each of the wake/sleep stages. RTs were measured with a precision of 1 ms.

Spline and Current Source Density Mapping

A primary purpose of this experiment was to compare the scalp distribution maps for N1b, P2 and the difference waveform, wNd. The wNd wave was computed by subtracting point-by-point the ERP waveform elicited by the standard stimuli recorded during Stage 2 sleep from that recorded during Wakefulness. Since the physical stimulus was constant between waking and definitive sleep (Stage 2), the difference wave should reflect the differential processing that occurs in the waking state. Spline and current source density maps were computed using the grand averaged data.

Spline Potential Mapping: Scalp voltage ERP data were produced as two-dimensional spline potential (SP) maps (Perrin et al., 1987) for peak N1b and P2 data during Wakefulness and for the wNd-early and wNd-late waves. There is some controversy in the literature concerning the precise time interval to be employed for mapping. Some authors average over several data points while others employ a specific peak value. Since Giard et al. (1988) opted for the peak value (i.e., the point in time at which a peak reaches its maximum value), this method was also employed in the present study. Inter-electrode values were interpolated based on

the actual data recorded from the 29 electrode sites. Thus, the inter-electrode space was filled with derived (or "interpolated") values. The choice of the reference site has important consequences on voltage distribution maps. An "inactive" reference site provides the best representation of the EEG signal (Picton et al., 1995). No reference is, however, truly inactive. Thus, although a nose reference was employed in the present study, it is still sensitive to the electrical activity of the brain. Although other reference sites, most notably the mastoid and earlobe, have been employed in the literature, none can be demonstrated to be truly neutral. Scalp distribution maps may vary simply because of the choice of the reference depending on the extent of its activity and the orientation of the source dipole under consideration. Some researchers, therefore, choose to use a so-called "averaged" reference. The averaged reference is claimed to be the best estimate of an inactive reference (Bertrand et al., 1985). The average voltage across all electrodes (which should approximate zero-voltage) is then subtracted from each of the active electrodes. Since the resultant values will be identical regardless of the actual reference, this technique is also called "reference-free" recording (Lehmann and Skrandies, 1980; Bertrand et al., 1985). Both methods were employed in the present study. Thus, maps were constructed when the nose was used as a reference and also when an average reference was used.

Current Source Density Mapping: The current source density (CSD) maps were derived using a Laplacian transformation of the scalp-recorded ERP data. CSD maps do not depend on assumptions of either the relevant brain generators or of the homogeneity of the volume conductors (Perrin et al., 1987, 1989; Picton et al., 1995). Since the CSD distributions have peaks and troughs which are sharper than those of the spline potential fields, CSD maps can spatially and temporally separate distinct current sinks and sources (as negative and positive potentials respectively) from the smeared potential distributions recorded from simultaneously active neural structures (Perrin et al., 1987; Giard et al., 1988; Picton et al., 1995). Thus, CSD maps can provide a better estimate of the number and orientation of the intracerebral generators which may overlap in the scalp recorded potential fields. Moreover, CSD maps are more sensitive to the depth of the brain generators than are the spline interpolation maps. Thus, CSD maps can help to distinguish between activity arising from a deep-seated dipole generator from activity arising from more superficial cortical generators.

Results

The sleep onset latencies (defined as the delay from the start of stimulus presentation to the start of Stage 1 sleep)

ranged from 447 s (SD=255 s) during the first SO period to 134 s (SD=65 s) during the last SO period. With repeated awakenings, there was no general trend among the replications toward a shorter SO time. Overall, the mean SO latency was 212 s (SD=185 s). The mean number of averaged trials per subject within Wakefulness, Stage 1 and Stage 2 of sleep was 1547, 619 and 2272 respectively, collapsed over the entire testing period.

Behavioural Data

Correct behavioural responses to the rare tones occurred on 94.4% of trials during the Wakefulness condition. Correct detections during Stage 1 sleep were made on 47.0% of trials, and dropped to 3.0% during Stage 2 sleep (see Table 4.1). Reaction time to detected targets was prolonged as subjects became more drowsy as they moved from Wakefulness to Stage 1 sleep. During Stage 1 sleep, there was increased variability in subjects' detection rates, ranging from a low of 4% in one subject to as high as 78% in another. During Wakefulness and Stage 2 sleep, the variability of responses was much lower as subjects correctly identified almost all target stimuli during Wakefulness and almost none during Stage 2 sleep.

------- Insert Table 4.1 about here -------

ERPs Elicited by Target Tones

During Stage 2 sleep, for individual subjects, the peak of P3 was difficult to discern relative to the background noise. It was, therefore, measured as the average of all data points between 300 and 500 ms. Mean P3 amplitude and standard error values recorded at Fz, Cz and Pz for each wake/sleep stage for both detected and missed targets is found in Table 4.2. Midline ERPs (Fz, Cz, Pz) recorded to detected target tones during Wakefulness and Stage 1 sleep (there were too few trials to include Stage 2 sleep) are illustrated in Figure 4.2. P3 to the detected targets did not significantly differ in either latency or amplitude during Wakefulness and Stage 1 of sleep.

------- Insert Table 4.2 and Figure 4.2 about here -------

There were a number of targets that were not detected (i.e., misses) during Stage 1 sleep. Overlapping ERPs recorded at the midline electrode sites, to detected and missed targets can be seen Figure 4.3. A reduced amplitude P3 wave was still apparent to missed targets. This P3 was not significantly prolonged, but was significantly attenuated relative to that observed following detected targets [$F(2,16)=9.77$, $p<0.01$].

------- Insert Figure 4.3 about here -------

It is possible that a late positive wave could occur to any

rare stimulus during sleep whether it was detected or not. The P3 to misses in Stage 1 was therefore compared to that observed occurring to misses during Stage 2 sleep. This is illustrated in Figure 4.4. P3 was not apparent in Stage 2 sleep. It was, therefore, significantly attenuated compared to that occurring for missed targets during Stage 1 [$F(2,16)=10.52$, $p<0.01$].

------- Insert Figure 4.4 about here -------

ERPs Elicited by Frequent Tones

The grand averaged waveforms during Wakefulness are shown in the left hand portion of Figure 4.5. A zoom of Cz, T7 and the left mastoid (M1) waveforms are presented in the right-hand portion of the figure. The central N1 (or "N1b") inverted in polarity at the mastoid. A longer latency "N1c" is apparent at temporal sites.

------- Insert Figure 4.5 about here -------

Figure 4.6 illustrates the grand averages following the frequent stimulus during Wakefulness, Stage 1 and Stage 2 of sleep. A zoom of the Cz grand average is presented in the right hand portion of the figure. P1, N1b, N1c (measured at the left and right temporal sites), P2 and N2 peaked at 48, 93, 129, 182 and 280 respectively during Wakefulness and at 52, 103, 115, 193 and 306 ms respectively during Stage 2 of sleep. There were no

significant latency changes in either P1, N1b, or P2 from Wakefulness to Stage 1 and again from Stage 1 to Stage 2 of sleep.

------- Insert Figure 4.6 about here -------

Mean amplitudes recorded from the midline electrode sites, for the P1, N1b, N1c (left and right temporal sites), P2 and N2 ERPs elicited by standard stimuli during each stage of the wake/sleep cycle are presented in Table 4.3. A significant electrode site by sleep stage interaction was observed for the amplitude of P1 [$F(4,32)=9.32$, $p<0.01$]. P1 was significantly larger (more positive) during Stages 1 and 2 of sleep compared to Wakefulness. Differences were most evident at the frontal and central scalp sites. Differences at the parietal scalp site only became significant when Wakefulness was compared to Stage 2 sleep.

------- Insert Table 4.3 about here -------

A significant electrode site by sleep stage interaction was observed for the amplitude of N1b [$F(4,32)=7.50$, $p<0.01$]. Follow-up analysis indicated N1b was significantly smaller (less negative) during Stages 1 and 2 of sleep compared to Wakefulness. These differences were significant at the frontal and central scalp sites. ERP changes at the parietal site were significant

between Wakefulness and Stages 1 and 2 of sleep. No differences were observed between Stages 1 and 2 at the parietal site.

A significant latency effect was found for peak N1c (measured at T7) [$F(2,16)=5.04$, $p<0.05$]. N1c occurred earlier during Stage 2 sleep (115 ms) compared to both Wakefulness (129 ms) and Stage 1 sleep (132 ms). A significant amplitude main effect was also noted [$F(2,16)=21.19$, $p<0.01$]. N1c became significantly smaller (less negative) as subjects moved from Wakefulness (-1.62 μV) to Stage 1 sleep (-0.60 μV) and again from Stage 1 sleep to definitive Stage 2 sleep (0.38 μV).

A significant electrode site by sleep stage interaction was observed for the amplitude of P2 [$F(4,32)=16.52$, $p<0.01$]. At all midline electrode sites, P2 became significantly larger (more positive) as subjects moved from Wakefulness into Stage 1 sleep. P2 became significantly larger between Stages 1 and 2 of sleep at Fz and Pz only.

Peak N2 was significantly delayed from Wakefulness to Stage 2 of sleep [$F(2,16)=7.47$, $p<0.01$]. N2 latency was significantly delayed in Stage 2 sleep (306 ms) compared to both Wakefulness (280 ms) and Stage 1 sleep (285 ms). A significant electrode site by sleep stage interaction was observed for N2 amplitude [$F(4,32)=7.75$, $p<0.01$]. N2 was significantly larger (more negative) during Stages 1 and 2 of sleep compared to Wakefulness. During Wakefulness and Stage 1 of sleep, Fz and Cz were significantly more negative than Pz. During Stage 2 of sleep, however, Cz was significantly more negative than both Fz and Pz.

Topographic Comparisons

The waking negative difference (wNd) waveform, derived by subtracting the Stage 2 sleep ERP waveform from the Waking ERP waveform, is illustrated in Figure 4.7. The wNd wave appeared as a long-lasting negative slow wave (measured at Cz as a 25% difference from baseline) beginning at 33 ms and returning to baseline at 243 ms. The wNd wave consisted of two subcomponents, an early fronto-central wave peaking at 95 ms and a later more centrally distributed wave peaking at 205 ms. The early and late peaks of the wNd waveform overlapped both spatially and temporally with the N1b and P2 peaks recorded during Wakefulness (see Figure 4.8).

------- Insert Figures 4.7 & 4.8 about here -------

During Wakefulness, both N1b and the early wNd waves were maximal over fronto-central areas of the scalp. Both inverted in polarity at the mastoid and at the lateral, parietal sites (P7/P8, P9/P10). Spline maps were initially constructed using a nose reference. Since both N1b and the early wNd waves reached maximum amplitude at about 93 ms, the maps were computed at this point in time. For presentation of the maps, the head is tilted 30° from the sagittal, inferior-superior axis to provide a view of the top of the head and 20° from the coronal, anterior-posterior axis to provide a view of the most of the left side of the head and a limited view of the right side. Negative voltages

are indicated by the dashed lines and positive voltages by the solid lines. The thick solid line represents the spatial location of a change from negative to positive voltage. The upper portion of Figure 4.9 presents the spline potential contour maps computed for N1b and the early wNd using the nose reference. Each contour represents a 0.25 μV change in voltage. Reference-free (or averaged reference) spline maps were also constructed (see the middle portion of Figure 4.9). The iso-potential zero voltage spatial location moved in an anterior-superior direction from a from a T7/Pz-Oz/T8 plane when the nose reference was used to a C3-T7/Pz/C4-T8 plane when the averaged reference was used. The N1b and early wNd maps were essentially identical, regardless of which reference technique was employed.

Following a Laplacian transformation of the data, CSD maps were then computed. CSD maps display the spatial and temporal ERP activity as distinct current sources and sinks which appear "smeared" in the voltage distribution maps and therefore, lose distinction. The CSD maps are thus able to provide an estimation of the number of intracerebral sources and their orientation. The CSD maps for N1b during Wakefulness and the early wNd wave are illustrated in the bottom portion of Figure 4.9. A focal bilateral, symmetrical sink was located at FC3 and contralaterally at FC4 (not seen in the Figure). Source activity appears centred at T7/T8. Again, the N1b and early wNd maps appear essentially identical.

There is debate in the literature about whether the N2

observed during wakefulness and the N2 observed during sleep represent the same intra-cerebral process. To address this controversy, maps were constructed for the waking and sleeping N2 using both a nose and an average reference (see Figure 4.10). The peak of N2 occurred later during Stage 2 than during Wakefulness. Because of this latency difference the Waking N2 map was constructed at 280 (actual 281.3 ms), and the Sleeping N2 map was constructed at 306 (actual 304.7 ms). The Waking and Sleep N2 maps were quite different. The Waking N2 appeared to be focussed over frontal regions of the scalp, changing to positive voltage over central and posterior regions. The sleeping N2 showed a sharp vertex focus. No positive voltages were apparent over the scalp. Of course, when an averaged reference was employed, the negative-positive distribution was altered. Nevertheless, the N2 map observed in the Waking state was quite different from that observed during sleep.

------- Insert Figure 4.10 about here -------

A P3 was observed to detected targets during Wakefulness and Stage 1 sleep. To verify if the P3 recorded during Stage 1 had the same topography as that in the Waking state, spline maps using both a nose and an average reference were constructed (see Figure 4.11). P3 was largest in parietal regions in both states. For this reason, the head was tilted 20° from the vertical, inferior-superior axis to provide a view of the back of the head

and 20° from the horizontal, anterior-posterior axis to provide a significant view of the left side of the head and a limited view of the right side. Each contour now represents a 1.00 μV change in voltage. The positive voltage activity is centred at Pz and decreases proportionately toward the fronto-temporal electrode sites. This focal positivity located at Pz is evident in all of the P3 maps during Wakefulness and Stage 1 of sleep. Thus, these maps appear essentially identical.

------- Insert Figure 4.11 about here -------

The P3 to undetected targets during Stage 1 was unexpected. To determine if this P3 was similar to that for detected targets, iso-potential voltage distribution maps were again computed (see Figure 4.12). Since the P3 to undetected targets was significantly attenuated, the contour maps were constructed to reflect this relative difference in voltage dispersion. Each contour represented a 1.0 μV change for the detected maps but only 0.5 μV change for the undetected target maps. Again, the positive voltage activity is centred at Pz and decreases proportionately toward the fronto-temporal electrode sites. This focal positivity located at Pz is evident in each of the P3 maps (detected and missed target tones) during Stage 1 of sleep. Again, these P3 maps appear essentially identical.

------- Insert Figure 4.12 about here -------

Discussion

Behavioural performance, measured as the number of correct target stimulus detections, significantly declined from Wakefulness to Stage 1 sleep. Almost no responses were recorded during Stage 2 sleep. This is in agreement with previous behavioural studies (Noldy et al., 1988; Ogilvie et al., 1984; 1989; 1991; Harsh et al., 1994). RT slowed with increasing sleepiness. This again replicates previous studies (Noldy et al., 1988; Ogilvie et al., 1989, 1991; Harsh et al., 1994). Subjects correctly identified almost all target stimuli during Wakefulness and almost none during Stage 2 sleep. Stage 2 therefore appears to represent the definitive time of "loss of consciousness".

The amplitude of N1b decreased from Wakefulness to Stage 1 and was near baseline level in Stage 2 of sleep, confirming previous findings (Noldy et al., 1988; Nielsen-Bohlman, 1991; Ogilvie et al., 1991; de Lugt et al., 1996). The decrease in N1 amplitude was parallelled by a gradual increase in P1 and P2. When peak-to-peak amplitudes (P1-N1b and N1b-P2) were measured, no significant differences emerged. It is, therefore, not N1b per se that is affected by sleep onset. Rather, a slow negative wave that overlaps the P1-N1b-P2 waking waveform is removed at sleep onset. The additional negativity associated with the waking waveform has been labelled the Waking Negative Difference (wNd) wave (Campbell et al., 1992), to distinguish it from the negative difference wave (Nd) wave observed in studies of selective attention (Hansen & Hillyard, 1980). Näätänen and Picton (1987)

have interpreted sleeping data in an opposite manner; a slow *positive* wave is *added* to the sleeping waveform. Whether a negative wave is added to the Waking ERP or a positive wave is added to the sleeping ERP is not a trivial point. It is similar to the arguments that have been raised in studies of selective attention. Is a negative wave added to the attended ERP or is a positive wave added to the unattended ERP?

N1b and wNd both peaked at around the same point in time (about 93 ms) and both potentials inverted in polarity at the mastoid. The inversion of the wNd wave at the mastoid when a nose reference is used is in contrast to the lack of an inversion of the Nd wave reported in studies of selective attention (Alho et al., 1986; Giard et al., 1988; Teder et al., 1992). In these selective attention studies, the difference between attended and unattended ERPs (i.e., Nd) was considerably smaller that the difference observed between the Waking and Stage 2 ERPs (i.e., wNd).

Previous studies of attention have indicated that N1b and Nd are independent components. Maps of N1b and Nd were different in Waking subjects (Giard et al., 1988). In the present study, the voltage distribution maps (using either a nose or an average reference) were very similar having peak negativity at Fz/Fz-Cz, which inverted in polarity at the mastoids sites. Moreover, CSD maps for N1b and wNd were also very similar. Both showed clear bilateral sink activity at FC3 and FC4 and bilateral source activity at T7/T8 and at P7/P8. Thus, in the present study, there

is little evidence to support the independence of N1b and wNd. A radical and novel interpretation of the role of N1b therefore is deemed to be warranted. It appears that the N1b observed during Wakefulness is entirely *endogenous*. In studies of selective attention, the large N1b observed during the Ignore condition, therefore, likely reflects an inability of subjects to ignore the auditory stimulus.

The most parsimonious explanation of wNd, therefore, is a marked decrease in the ability to sustain attention between the alert-waking and the drowsy-sleeping states (or that a slow positive wave is added to the waking ERP at sleep onset, possibly reflecting the inhibition of further information processing). Of course there are many physiological and biochemical changes that occur between the two states, any one of which might be used to explain wNd.

An examination of the grand averages indicates that wNd begins before the peak of P1, at approximately 30-40 ms following stimulus presentation. In selective attention tasks, Woldorff et al. (1987) indicated that Nd can also begin this early when a channel to-be-attended is easily discriminated from one to-be-ignored. Presumably, the physical characteristics of the stimulus are fully elaborated at this point in time. In this regard, the short-latency exogenous evoked potentials reflecting the extraction of physical characteristics of the stimulus are also relatively unaffected by sleep (Campbell and Bartoli, 1986; Bastuji et al., 1988).

N2 increased in amplitude as subjects moved from Wakefulness to Stage 2 of sleep confirming previous findings (Ornitz et al., 1967; Ogilvie et al., 1991; Harsh et al., 1994). The latency of the N2 response was also significantly delayed confirming previous findings (Kevanishvili and von Specht, 1979; Bartoli and Campbell, 1988; Broughton, 1988; Wesensten and Badia, 1988). This is in contrast to our previous study (de Lugt et al., 1996), when a fast rate of stimulus presentation was employed. With long inter-stimulus intervals a vertex sharp wave (Picton & Hillyard, 1974) or a K-Complex may be evoked in Stage 2 of sleep. The number of K-Complexes that are evoked increases as the ISI is lengthened (Bastien & Campbell, 1994). The N350 wave has been considered to be a sub-component of the K-Complex. The inclusion of at least some K-Complexes in the ongoing sleep onset averages may have produced an apparent enhancement of N2. The speeded rate of stimulus presentation used in our previous study (de Lugt et al., 1996) may have reduced the number of evoked K-complexes included in the average, thus decreasing the amplitude of the N2 potential.

The N2 recorded during Stage 2 appears to be a different component than the N2 recorded during Wakefulness. This claim is supported by the dissimilarity of the topographical maps. During Wakefulness, the relatively small amplitude N2 activity was localized over the frontal regions. During Stage 2 sleep the much larger amplitude N2 was generalized over the entire scalp surface with a sharp, maximum peak focus at the vertex. Thus, the N2

recorded during Wakefulness is likely generated by different intra-cerebral sources than the N2 recorded during Stage 2 sleep.

The amplitude of the P3 response to the correctly detected target stimuli was not significantly different between Wakefulness and Stage 1 sleep. Moreover, the scalp distribution maps of the P3 following detected targets in the Waking state and Stage 1 sleep were essentially identical. The fact that subjects made overt detections during Stage 1 and that the P3 observed to these targets was identical to that observed in the Waking state provides very strong evidence of full conscious awareness during this apparent sleep state. A novel finding was the P3 that was observed to missed targets in Stage 1 sleep. This was not simply because of the rarity of the target. No P3 was apparent to undetected targets during Stage 2 sleep (Paavilainen et al., 1987; Campbell et al., 1992; Winter et al., 1995; Loewy et al., 1996). The P3 following the undetected target in Stage 1 was prolonged in latency and reduced in amplitude compared to detected targets. The scalp distribution maps for both were however, quite similar. The P3 following the undetected target may thus reflect conscious awareness of the stimulus, in spite of the failure to overtly respond. In the absence of a behavioural response, the prolongation and attenuation of the P3 is more difficult to interpret. P3 is reduced and prolonged in difficult discrimination tasks (Squires et al., 1973; Fitzgerald and Picton, 1983; Picton, 1992), perhaps reflecting uncertainty/equivocation. The attenuated P3 to missed targets may

thus be a reflection of uncertainty in the drowsy sleeper. Alternatively, the reduced P3 may be an artifact of averaging. On certain trials, it may be identical to the P3 elicited to detected targets. On other trials it may not be elicited as was the case during Stage 2 sleep. On average, P3 may appear to be reduced in amplitude.

The mapped P3 response to the detected targets in Wakefulness and to the detected and missed targets in Stage 1 sleep appeared to have a similar distribution of positive activity in each condition. Maximum positivity was observed at Pz in each map. Also, peak latency did not significantly differ between Wakefulness or Stage 1 sleep. Thus, it appears that it is the same P3 observed in Wakefulness as is observed in Stage 1 sleep regardless of subjects' behavioural response. The lack of a P3 response in Stage 2 of sleep confirms previous findings (Paavilainen et al., 1987; Campbell et al., 1992; Winter et al., 1995; Loewy et al., 1996). While this finding is suggestive that subjects were unconscious while asleep, the possibility that they were conscious yet distracted or inattentive cannot be discounted.

	Correct Detections (%)	Mean Reaction Time (ms)
Wakefulness	94.4 (3.4)	783.0 (24.7)
Stage 1	47.0 (9.3)	946.9 (27.0)
Stage 2	3.0 (1.4)	899.1 (27.6)

Table 4.1. Percentage of correct target detections and mean reaction time (in ms) for each sleep/wake stage (Wakefulness, Stage 1, Stage 2). Standard errors are presented in parentheses.

		Site	Mean Amplitude (μV)	Standard Error
Detected Targets	**Wake**	**Fz**	5.74	2.84
		Cz	11.62	3.14
		Pz	18.87	3.49
	Stage 1 sleep	**Fz**	6.29	2.32
		Cz	12.98	3.74
		Pz	17.00	3.76
	Stage 2 sleep	**Fz**	insufficient data	insufficient data
		Cz	insufficient data	insufficient data
		Pz	insufficient data	insufficient data
Missed Targets	**Wake**	**Fz**	insufficient data	insufficient data
		Cz	insufficient data	insufficient data
		Pz	insufficient data	insufficient data
	Stage 1 sleep	**Fz**	2.98	2.32
		Cz	6.90	2.70
		Pz	8.92	2.34
	Stage 2 sleep	**Fz**	-3.49	0.93
		Cz	-3.26	1.26
		Pz	-1.87	1.10

Table 4.2. Mean amplitude (in μV) and standard error for P3 elicited by target stimuli, for each wake/sleep stage (W, S1, S2). Data were quantified from Pz and were separated into correctly detected (Detected) targets and those which were not detected (Missed). P3 amplitudes recorded during Wakefulness and Stage 1 sleep were measured as the maximum positive peak between 300 and 500 ms post-stimulus. Amplitude values recorded during Stage 2 sleep were calculated as the average of all data points between 300 and 500 ms post-stimulus.

		Wakefulness	Stage 1	Stage 2
P1	Fz	0.64 (0.20)	1.38 (0.31)	2.16 (0.39)
	Cz	0.70 (0.24)	1.37 (0.35)	1.95 (0.37)
	Pz	0.35 (0.20)	0.53 (0.22)	0.69 (0.28)
N1b	Fz	-3.64 (0.79)	-1.89 (0.47)	0.81 (0.62)
	Cz	-3.43 (0.70)	-1.63 (0.50)	0.60 (0.64)
	Pz	-1.00 (0.57)	0.30 (0.78)	0.65 (0.52)
N1c	T7	-1.57 (0.38)	-0.55 (0.29)	0.31 (0.34)
	T8	-1.65 (0.49)	-0.65 (0.36)	0.44 (0.33)
P2	Fz	3.20 (0.58)	6.62 (1.13)	5.40 (1.36)
	Cz	4.58 (0.73)	8.04 (1.51)	7.43 (1.73)
	Pz	2.13 (0.41)	3.65 (1.03)	5.59 (1.36)
N2	Fz	-0.59 (0.71)	-5.00 (1.88)	-6.65 (1.68)
	Cz	0.52 (0.51)	-5.51 (1.86)	-9.62 (2.18)
	Pz	2.60 (0.56)	-0.40 (1.12)	-5.68 (1.41)

Table 4.3. Mean amplitude (in μV) and standard error (in parentheses) for each ERP deflection (P1, N1b, N1c, P2, N2) elicited by the standard stimuli. Data are provided for each stage of the sleep/wake cycle (Wakefulness, Stage 1, Stage 2).

FIGURE LEGEND

Figure 4.1 Topographical representation of the 29 electrode placements. The scale is linear along the lines radiating from the "pole" at the vertex of the map (Cz). The projection is extended down 20° beyond the equator which is drawn from Fpz to Oz to include the temporal electrodes T7 and T8. This plane corresponds approximately to the position of the Sylvian fissure. Sites inferior to the equator include F9/F10, P9/P10 and the two mastoids.

Figure 4.2 ERPs to detected target tones for Wakefulness (solid line) and Stage 1 sleep (dashed line) along the midline electrode sites (Fz, Cz, Pz). P3 is indicated by the open triangle.

Figure 4.3 ERPs to detected (solid lines) and missed (dashed lines) target tones recorded during Stage 1 of sleep. Waveforms are presented for the midline electrode sites (Fz, Cz, Pz).

Figure 4.4 ERPs to missed targets during Stage 1 (dashed lines) and Stage 2 (dotted lines) of sleep. Waveforms are presented for the midline electrode sites (Fz, Cz, Pz).

Figure 4.5 ERPs from the 29 scalp sites following the frequent stimuli during Wakefulness are presented in the left half of the Figure. A zoom of the vertex (Cz - solid line), left temporal (T7 - dotted line) and left mastoid (M1 - dashed line) waveforms are superimposed in the right half of the Figure. Note that the peak of N1b (Cz) is larger and earlier than the peak of N1c (T7), and is inverted at the mastoid (M1).

Figure 4.6 ERPs from 29 scalp sites following the frequent stimuli during Wakefulness (solid line), Stage 1 (dashed line) and Stage 2 (dotted line) of sleep is presented in the left half of the Figure. A zoom of the vertex electrode site can be seen in the right half of the Figure. N1 and N2 peaks are indicated by closed triangles, and P1 and P2 peaks by open triangles.

Figure 4.7 The wNd difference wave (computed by subtracting the waveform recorded during Stage 2 sleep from that recorded during Wakefulness).

Figure 4.8 Overlapping difference wave between Wakefulness and Stage 2 sleep (dotted line), and Wakefulness (solid line).

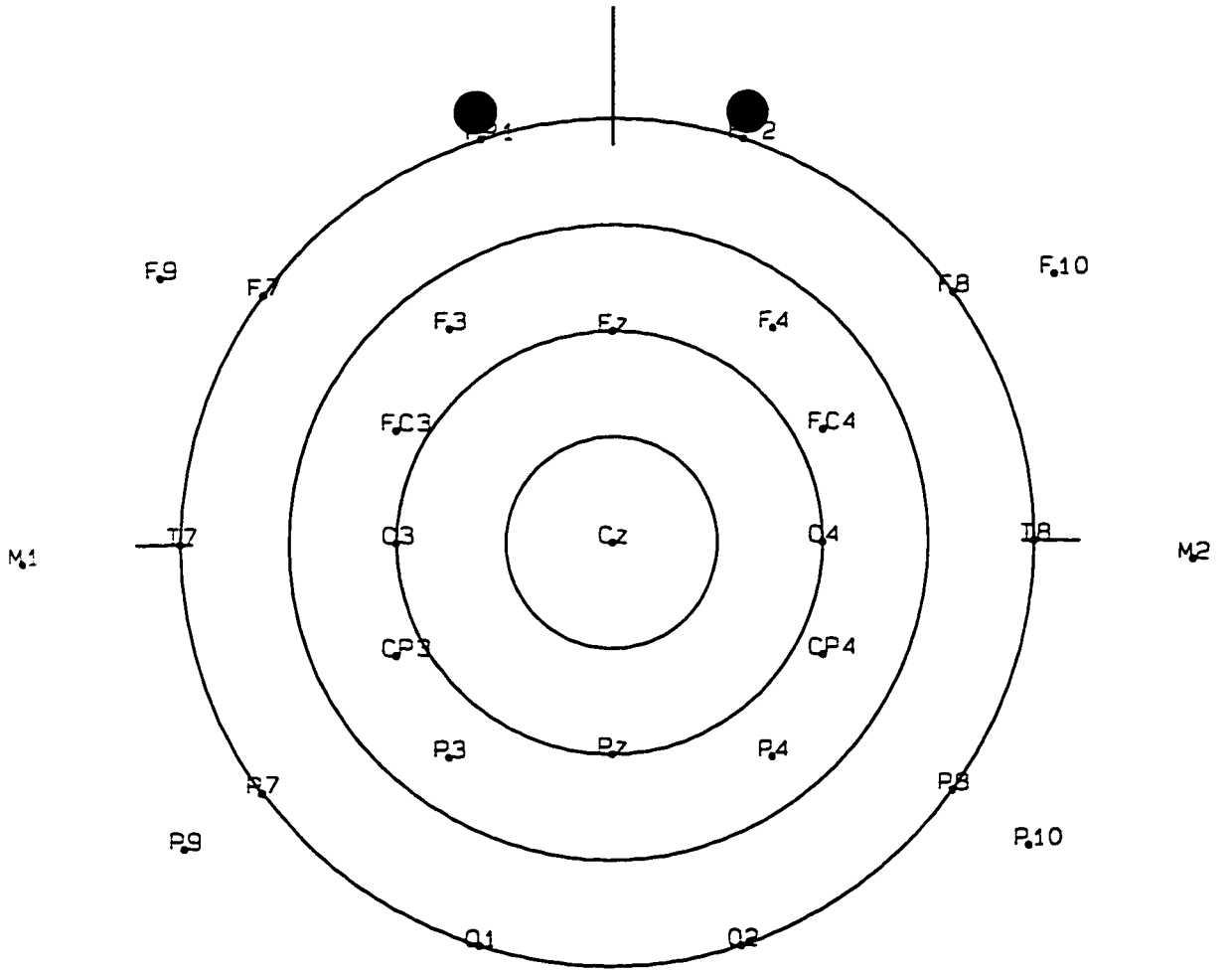
Figure 4.9 Topographical iso-potential maps of the N1 response recorded during Wakefulness (left side of Figure) and the wNd waveform (right side of Figure). Data are presented for the peak activity occurring at 93.8 ms. Each contour represents a 0.25 μV change in amplitude. Negativity is represented by dashed lines and positivity by solid lines. The thick solid line represents the changing of voltage polarity. Maps using a nose-reference are in the upper portion of the Figure and reference-free maps are in the middle portion.

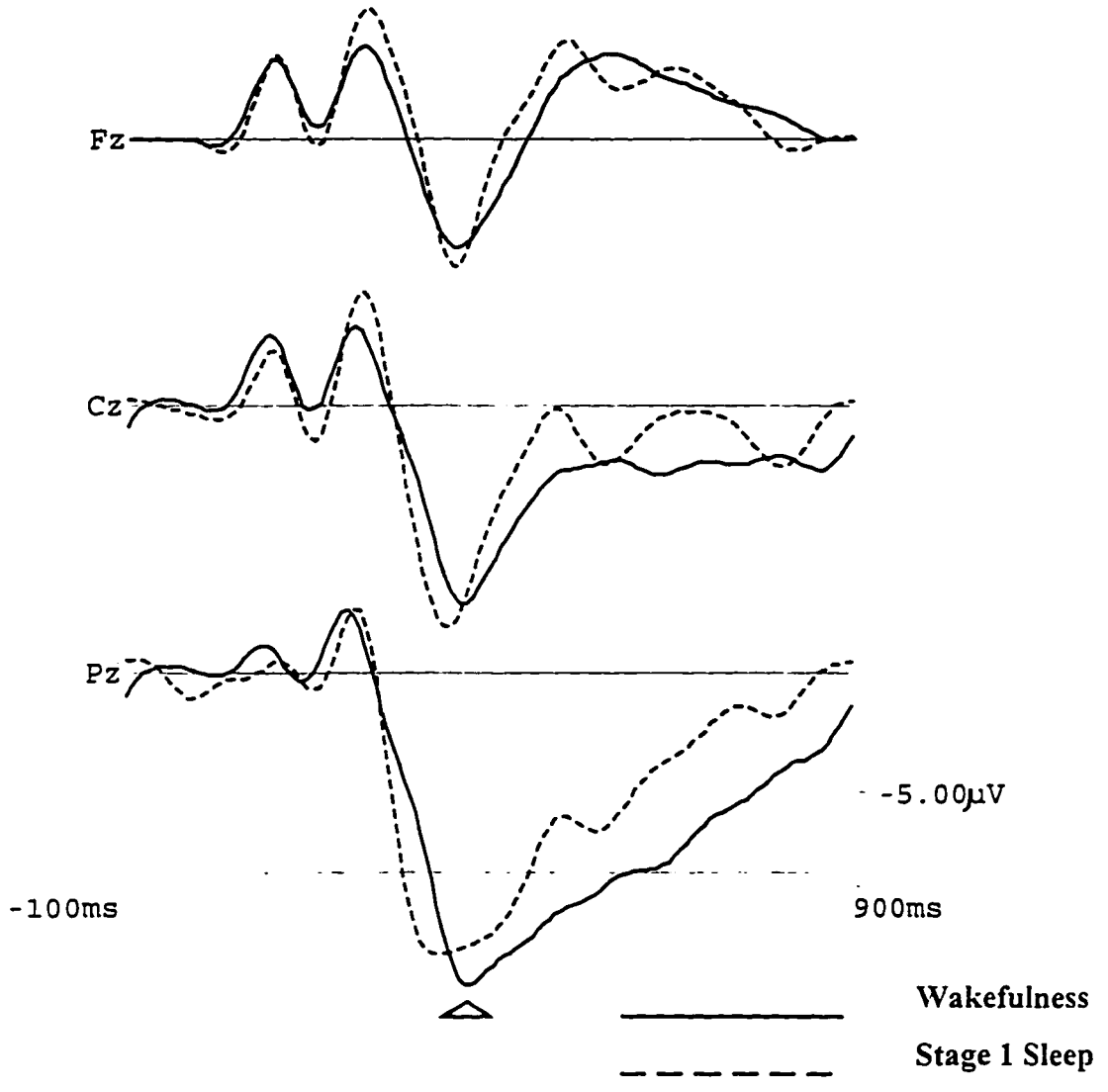
Current source density maps of the two waveforms can be seen in the lower portion of the Figure. The scale is 128 $\mu V/m^{-1}$. Sources are represented by solid lines and sinks by dashed lines.

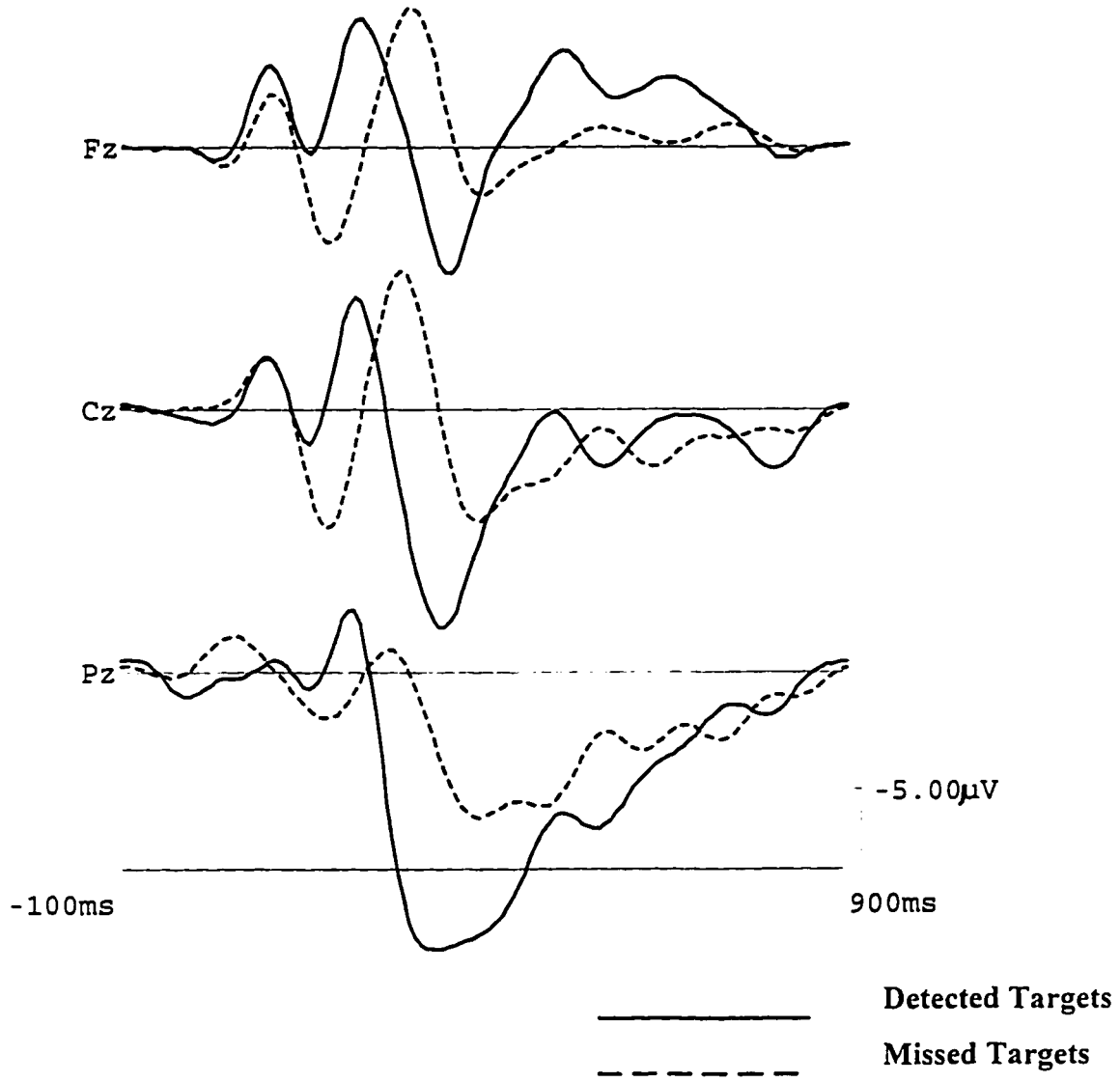
Figure 4.10 Topographical iso-potential maps of the N2 response recorded during Wakefulness (left side of Figure) and during Stage 2 of sleep (right side of Figure). Maps using a nose-reference are in the upper portion of the Figure and reference-free maps are in the lower portion. Maps are presented for the peak activity occurring at 281.3 ms for the Waking data and at 304.7 ms for the Stage 2 sleep data. Each contour represents a 0.25 μV change in amplitude. Negativity is represented by dashed lines and positivity by solid lines. The thick solid line represents the changing of voltage polarity.

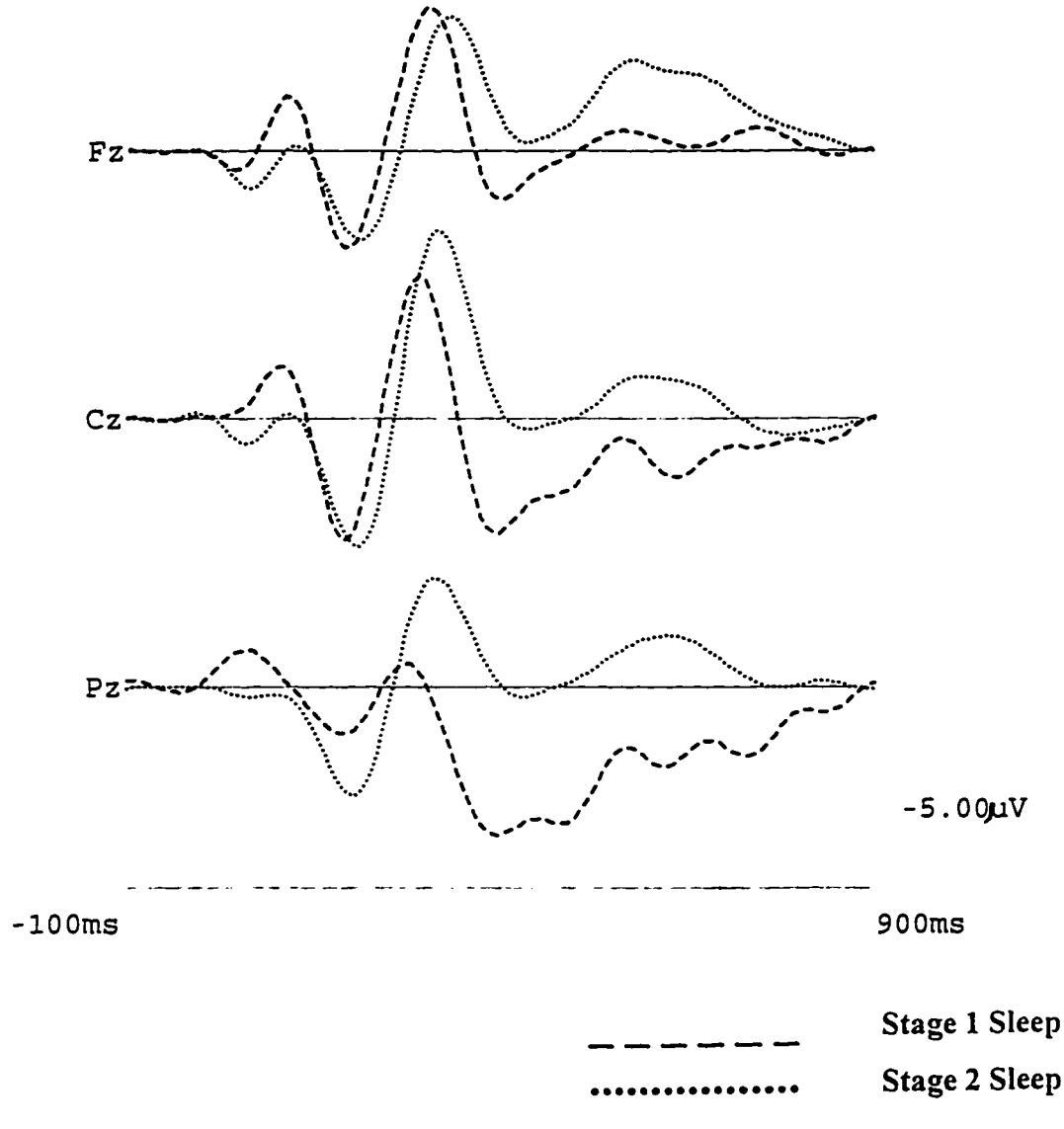
Figure 4.11 Topographical iso-potential maps of the P3 response during Wakefulness (left side of Figure) and Stage 1 of sleep (right side of Figure). Maps using a nose-reference are in the upper portion of the Figure and reference-free maps are in the lower portion. Maps are presented for the peak activity occurring at 343.8 ms for the Waking data and at 382.8 ms for the Stage 1 sleep data. Each contour represents a 1.00 μV change in amplitude. Negativity is represented by dashed lines and positivity by solid lines. The thick solid line represents the changing of voltage polarity.

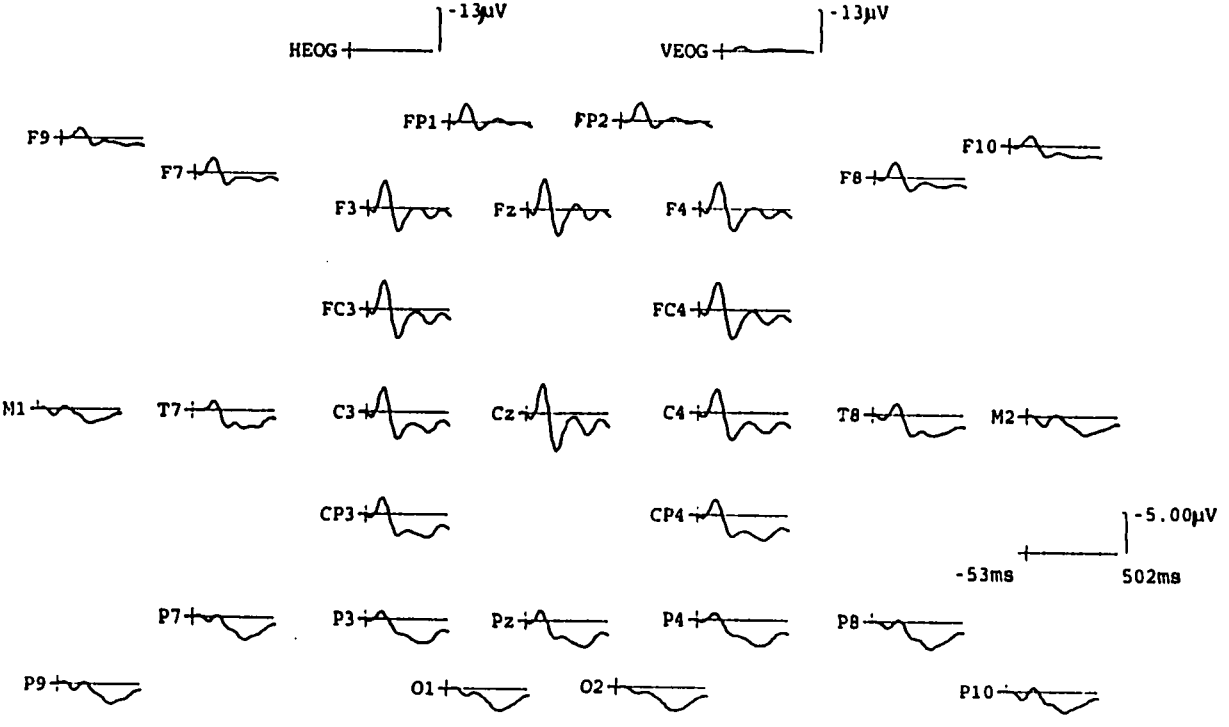
Figure 4.12 Topographical iso-potential maps of the P3 response to "hits" (left side of Figure) and "misses" (right side of Figure) during Stage 1 of sleep. Maps using a nose-reference are in the upper portion of the Figure and reference-free maps are in the lower portion. Maps are presented for the peak activity occurring at 382.8 ms for the P3 response to "hits" and at 406.3 ms for the P3 response to "misses". Each contour represents a 1.00 μV change in amplitude. Negativity is represented by dashed lines and positivity by solid lines. The thick solid line represents the changing of voltage polarity.

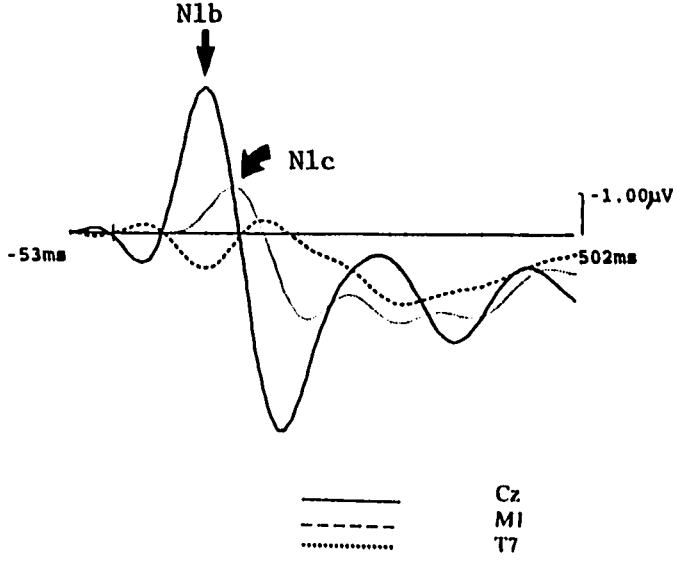

F9
F7
F3
Fz
F4
F8
F10
FC3
FC4
M1
T7
C3
Cz
C4
T8
M2
CP3
CP4
P3
Pz
P4
P7
P8
P9
P10
O1
O2

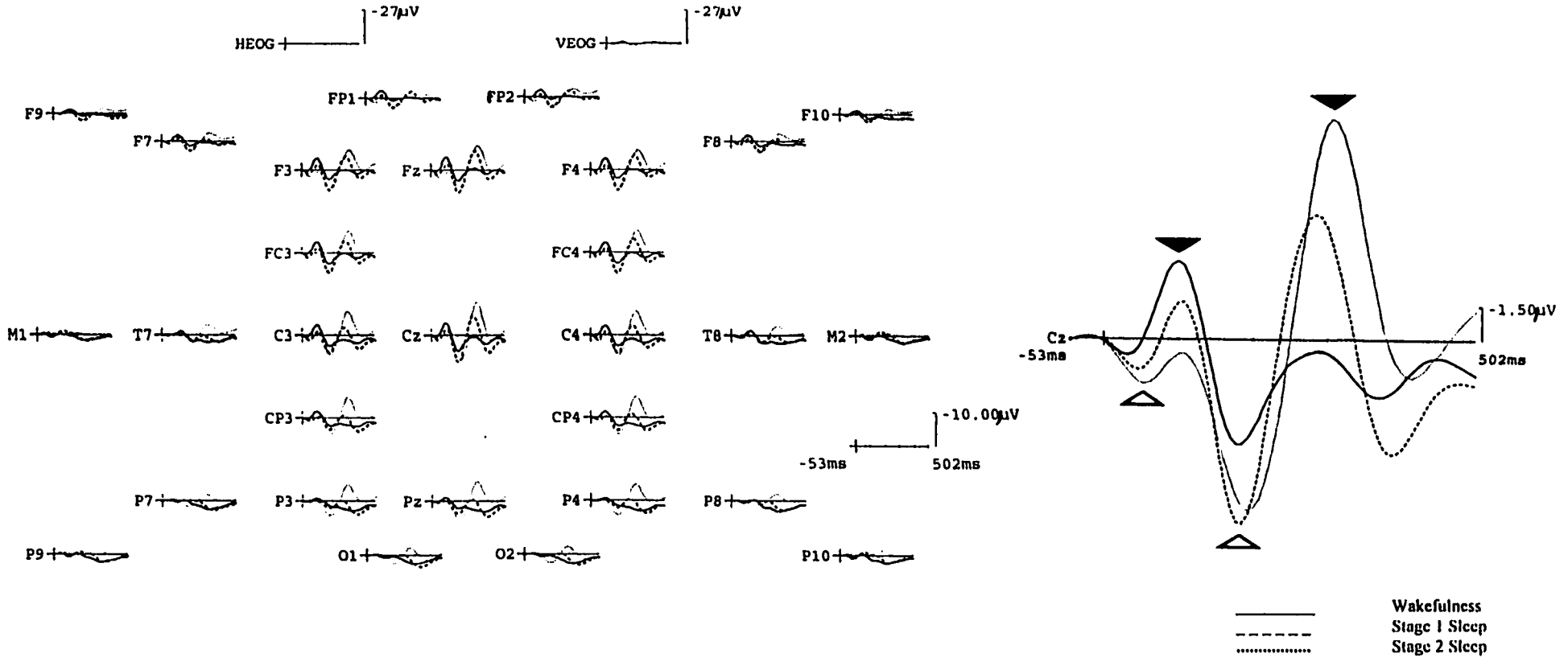

Fz
Cz
Pz
-5.00μV
-100ms
900ms
Wakefulness
Stage 1 Sleep

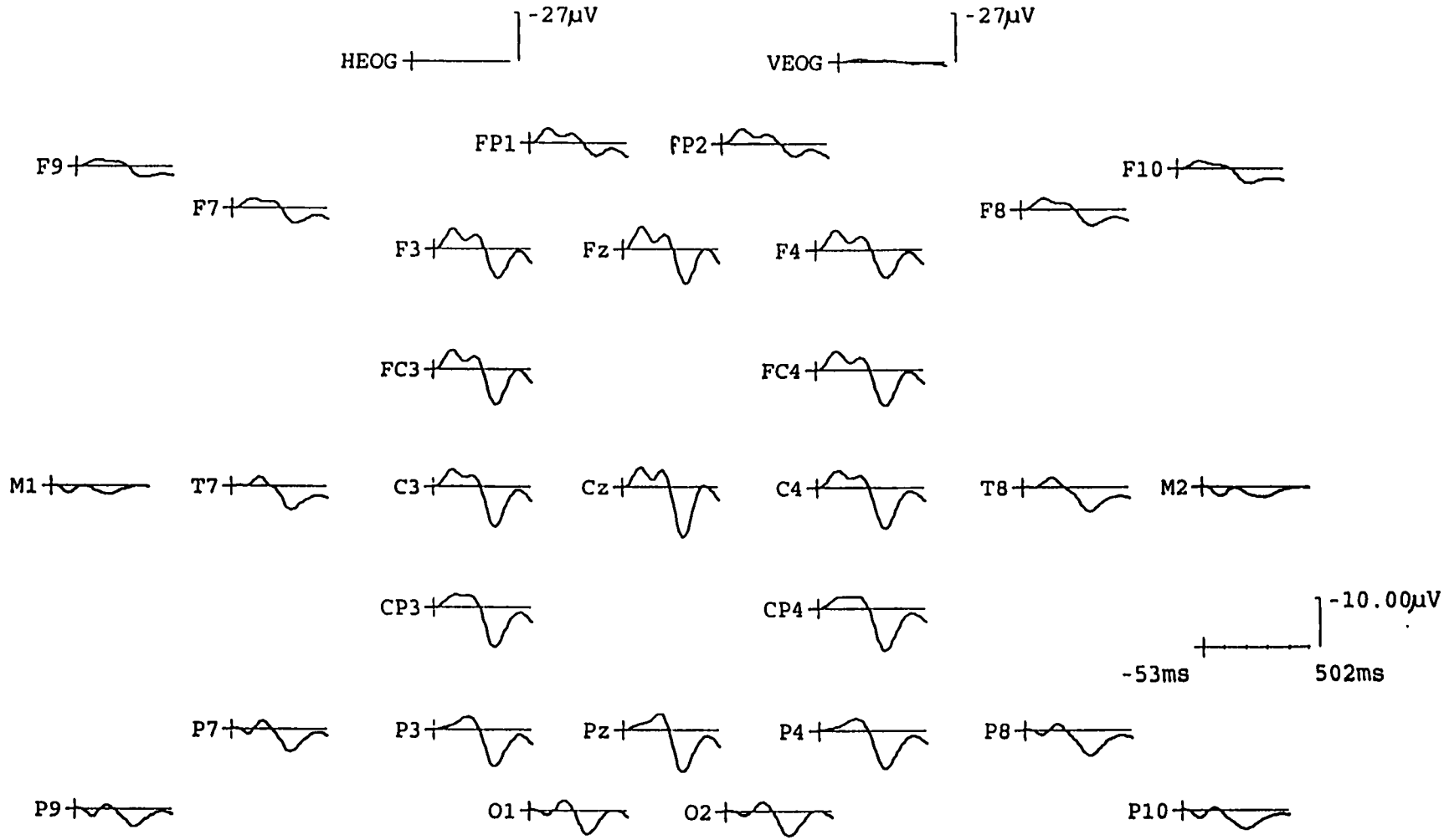

Fz
Cz
Pz
-5.00μV
-100ms
900ms
Detected Targets
Missed Targets

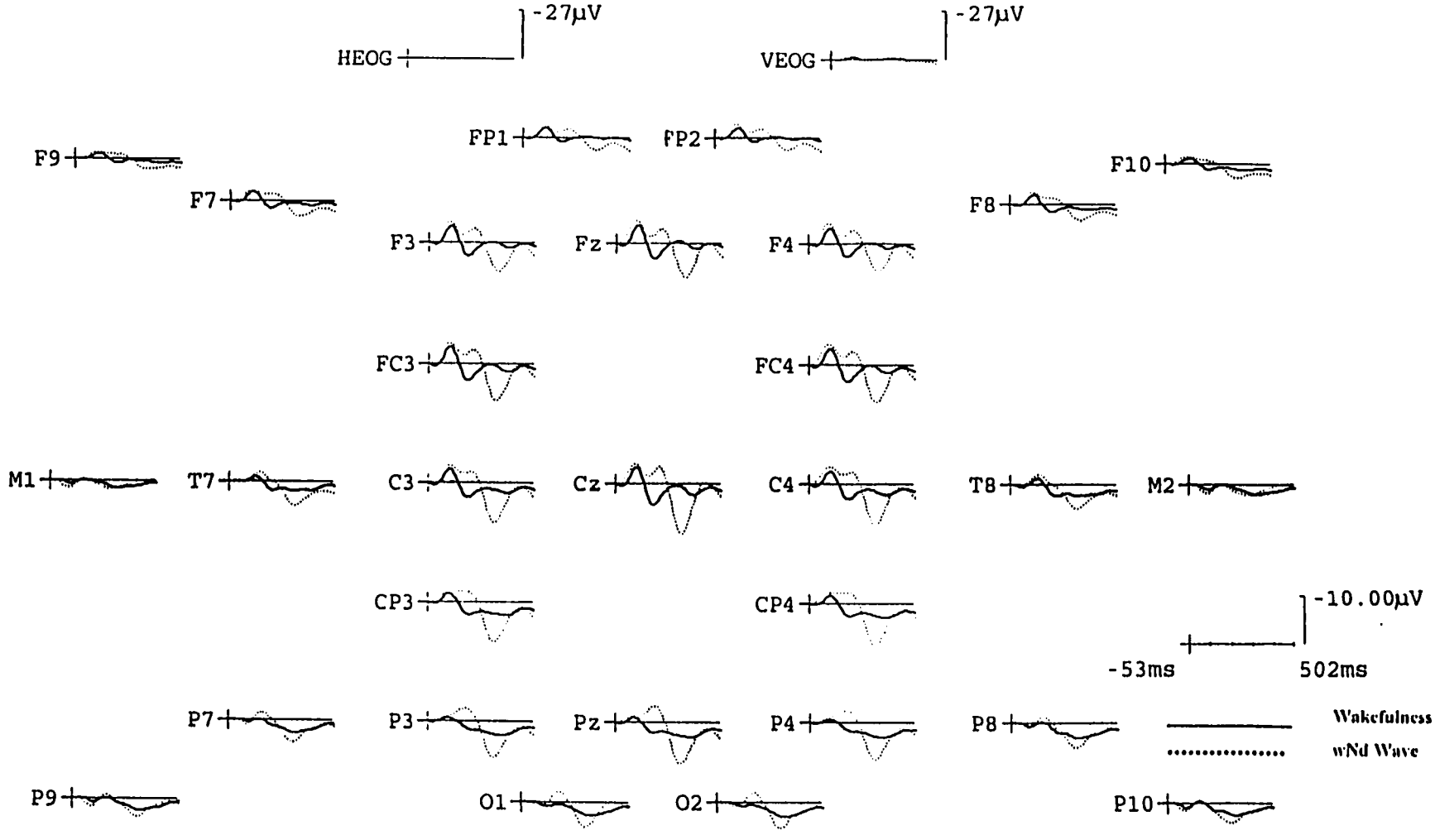

Fz
Cz
Pz
-5.00μV
-100ms
900ms
Stage 1 Sleep
Stage 2 Sleep

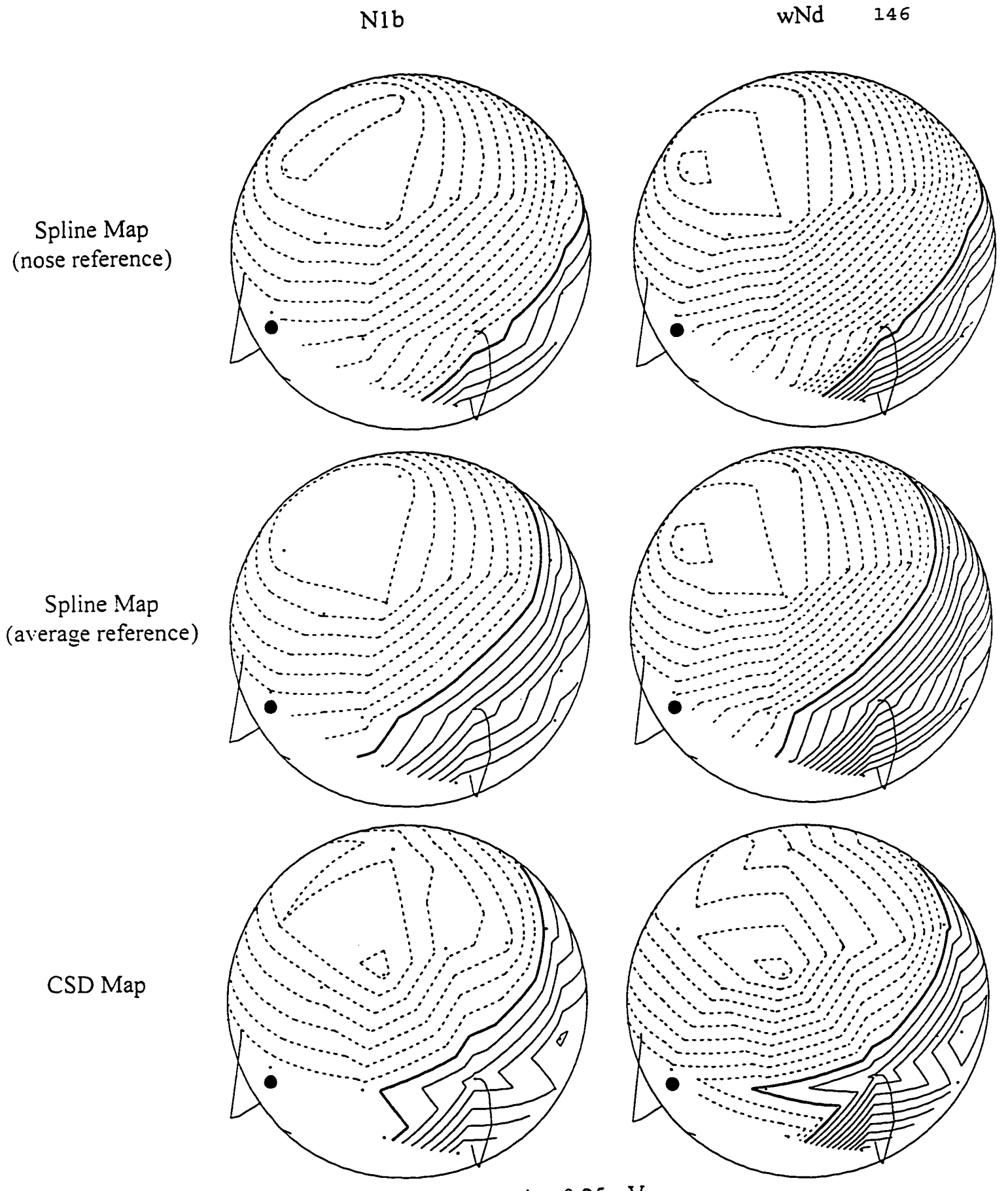

-13μV
HEOG
-13μV
VEOG
FP1
FP2
F9
F7
F3
Fz
F4
F8
F10
FC3
FC4
M1
T7
C3
Cz
C4
T8
M2
CP3
CP4
-5.00μV
-53ms
502ms
P7
P3
Pz
P4
P8
P9
O1
O2
P10


N1b
N1c
-1.00μV
-53ms
502ms
Cz
MI
T7


-27μV
HEOG
-27μV
VEOG
FP1
FP2
F9
F7
F3
Fz
F4
F8
F10
FC3
FC4
M1
T7
C3
Cz
C4
T8
M2
-10.00μV
-53ms
502ms
CP3
CP4
P7
P3
Pz
P4
P8
P9
O1
O2
P10
Cz
-53ms
-1.50μV
502ms
Wakefulness
Stage 1 Sleep
Stage 2 Sleep


-27μV
HEOG
-27μV
VEOG
FP1
FP2
F9
F10
F7
F8
F3
Fz
F4
FC3
FC4
M1
T7
C3
Cz
C4
T8
M2
-10.00μV
CP3
CP4
-53ms
502ms
P7
P3
Pz
P4
P8
P9
O1
O2
P10

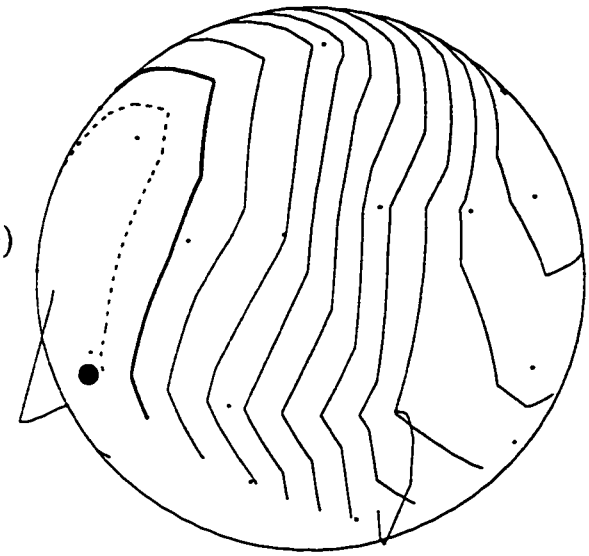

HEOG
-27μV
VEOG
-27μV
FP1
FP2
F9
F7
F3
Fz
F4
F8
F10
FC3
FC4
M1
T7
C3
Cz
C4
T8
M2
CP3
CP4
-10.00μV
-53ms
502ms
P7
P3
Pz
P4
P8
Wakefulness
wNd Wave
P9
O1
O2
P10

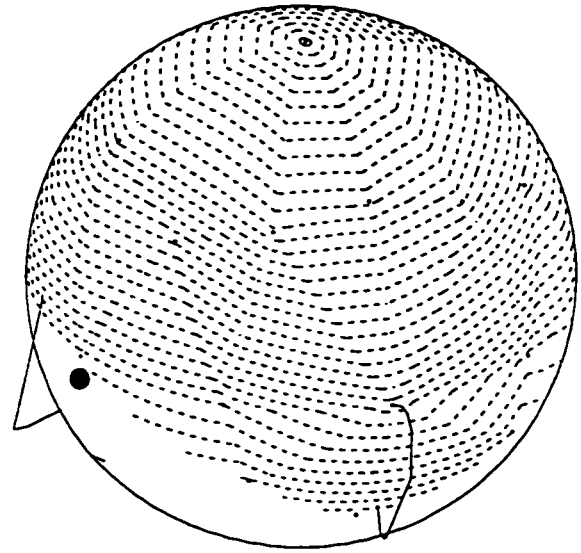

N1b
wNd
Spline Map
(nose reference)
Spline Map
(average reference)
CSD Map
Δ = 0.25 μV

N2 - Wake

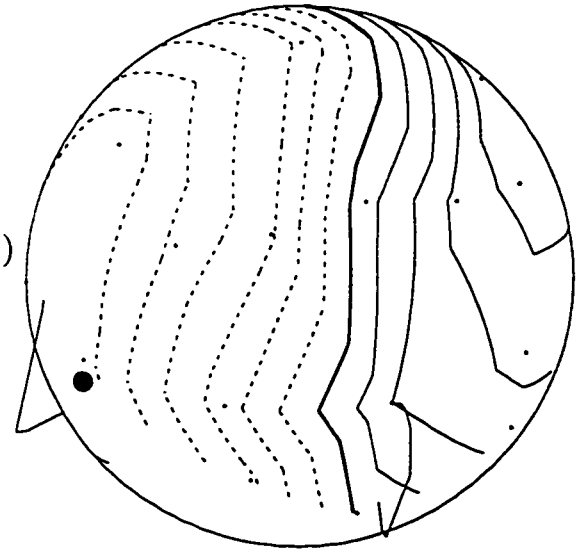
N2 - Stage 2

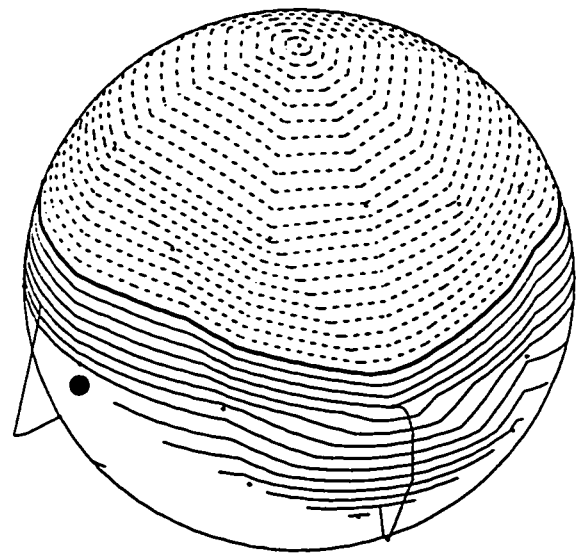
Spline Map
(nose reference)





Spline Map
(average reference)



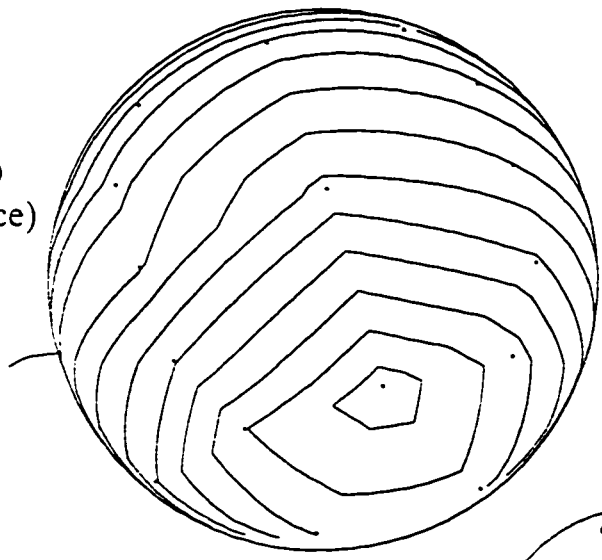


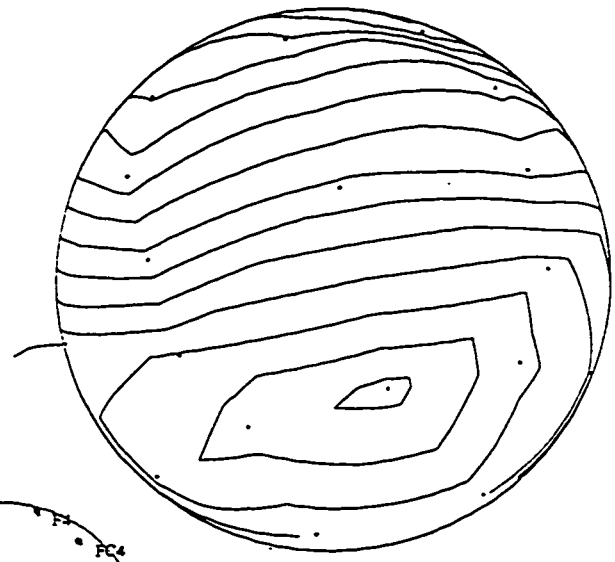
$\Delta = 0.25\ \mu V$

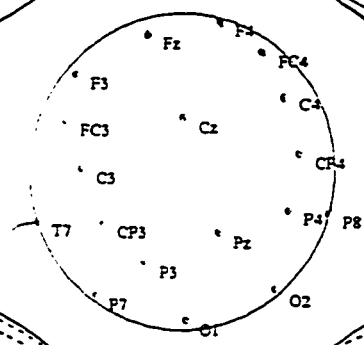
P3 - Wake

P3 - Stage 1

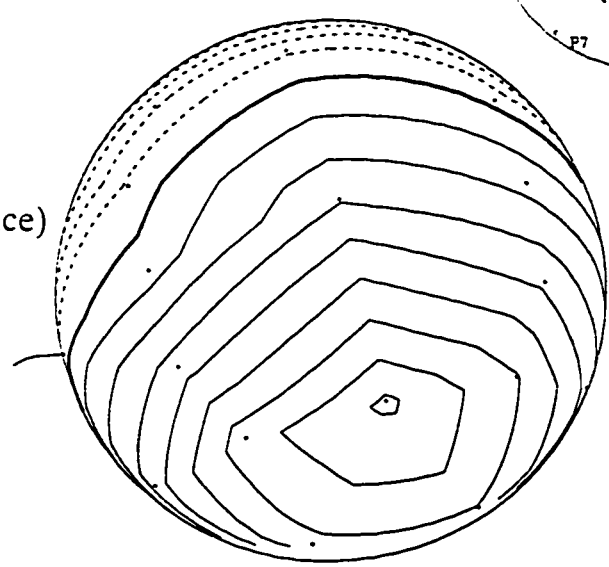
Spline Map
(nose reference)

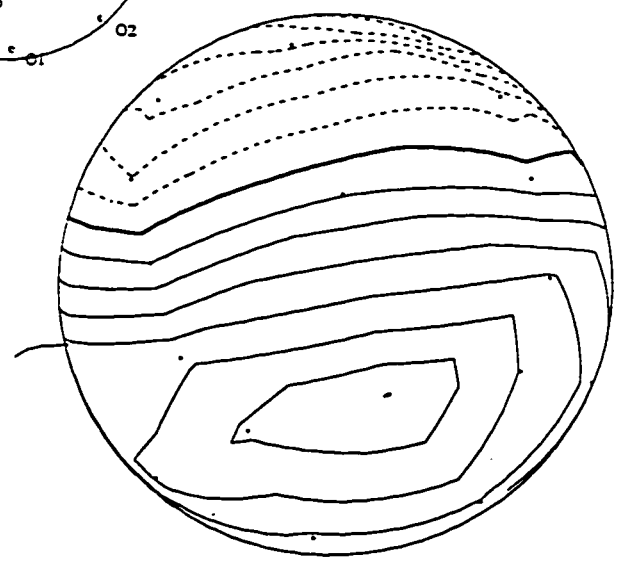






Spline Map
(average reference)



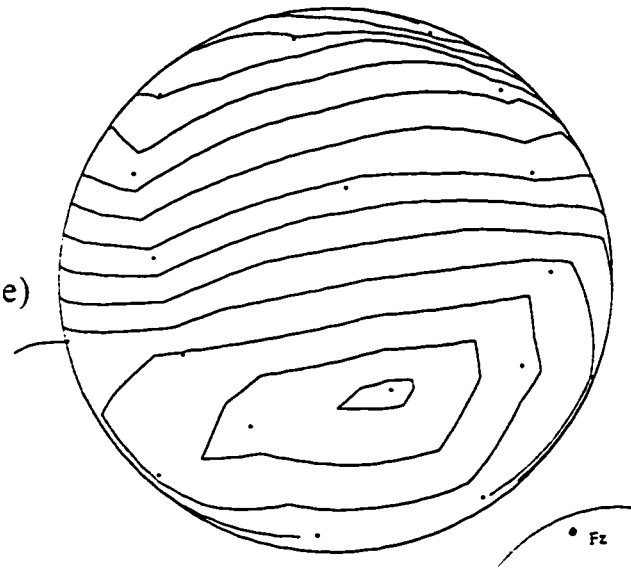


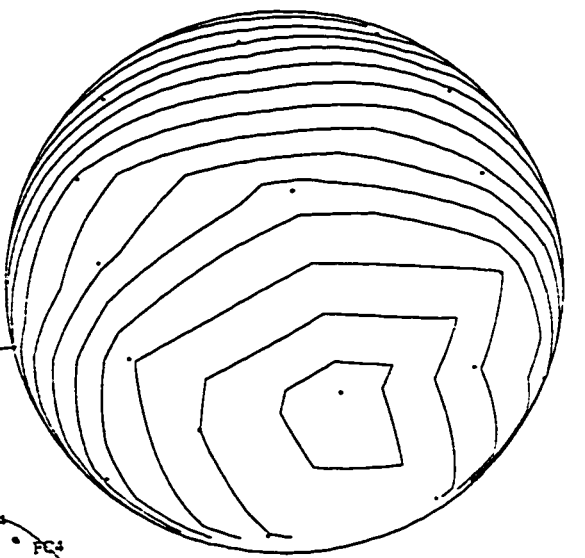
$\Delta = 1.0\ \mu V$

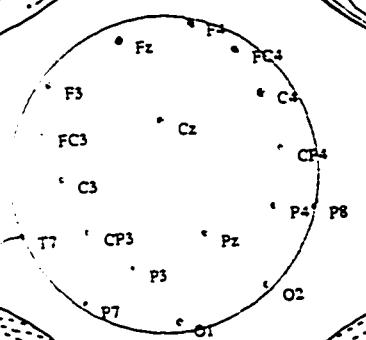
P3 - Stage 1 (hits)

P3 - Stage 1 (misses)

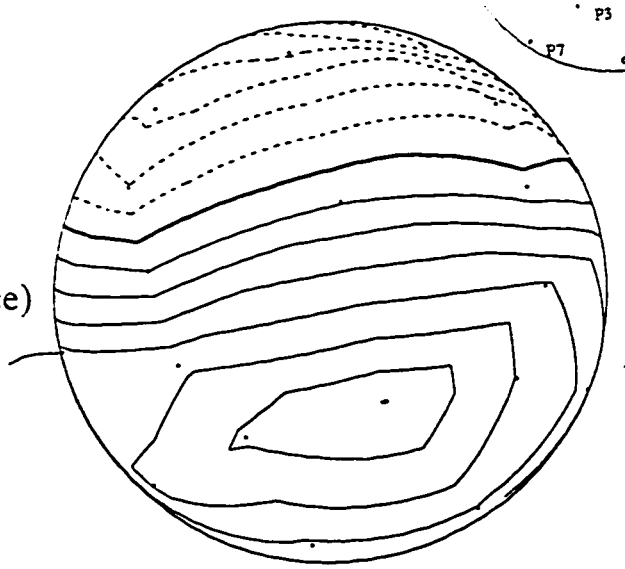
Spline Map
(nose reference)

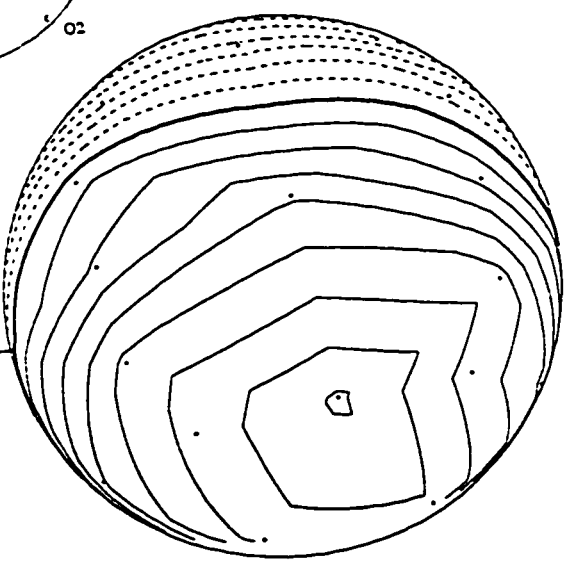






Spline Map
(average reference)





$\Delta = 1.0\ \mu V$

$\Delta = 0.5\ \mu V$

Chapter 5

GENERAL DISCUSSION, NOVEL FINDINGS AND CLAIMS

The purpose of this thesis was to explore the extent of information processing during the transition from a fully conscious state to one of unconsciousness. This problem has, of course, intrigued philosophers and scientists for centuries. The Introduction to this thesis pointed out some of the immense difficulties in solving the problem of consciousness. This thesis defined consciousness in different ways: (1) according to EEG criteria (is the subject awake-conscious or asleep-unconscious?); according to the subject's overt behavioural response (were conscious detections made?); (3) according to the presence or absence of a P3 (is there evidence of conscious awareness in the absence of a behavioural response?); and (4) according to the amplitude of the N1. The N1 wave was of particular interest in this thesis.

N1 was initially recorded in the 1950's. It has been the subject of much debate since that time. A great deal of research has examined the degree to which endogenous attentional and exogenous influences contribute to the waking P1-N1-P2 complex. N1 has been demonstrated to be affected by both the physical parameters of the stimulus and the psychological state of attention (consciousness) of the subject. As stimulus intensity increases or as the rate of stimulus presentation is slowed, N1 increases in amplitude. Similarly, N1 may increase in amplitude

as the subject becomes more attentive.

Some laboratories have attempted to separate exogenous and endogenous influences on N1 by employing selective attention tasks in which subjects were instructed to attend to stimuli presented in one channel (the Attend condition) and to ignore stimuli presented in the other (the Ignore condition). Evoked potential activity recorded to the stimuli in the Ignore condition were subtracted from those recorded in the Attend condition. The resulting long-lasting negativity is called the negative difference or Nd wave (Hansen and Hillyard, 1980). This Nd wave is thought to reflect the endogenous effect of attention and overlaps the exogenous N1 potential. The N1 seen in the Ignore condition is assumed by most authors to be entirely exogenous in nature, affected strictly by the physical parameters of the stimulus. In studies of selective attention, however, subjects may be unable to completely ignore stimuli presented in the to-be-ignored channel. The sleep period is the time when subjects are least attentive to, and thus least conscious of, their external environment. Therefore, the present series of experiments examined changes in the late auditory potentials at sleep onset - the transition from a period of full alertness and consciousness to a period of unconsciousness.

During the actual sleep period, P1 and P2 increase while N1 decreases in amplitude. The subtraction of the sleeping from the waking ERPs produces a long-lasting difference wave similar to the Nd wave observed in studies of selective attention. Campbell

et al. (1982) labelled this long-lasting slow negativity, the waking negative difference or wNd wave. This wNd wave is thought to reflect the additional processing a channel receives during the waking state. The remaining N1 potential observed during sleep may reflect the exogenous nature of the eliciting stimulus. Three experiments were designed to investigate changes to the N1 potential during the transition from the waking to the sleeping state. The initial studies were designed to solve a methodological problem in the literature. Some studies report that N1 is near baseline during Stage 1 of sleep while others report a much smaller change. A possible reason for this discrepancy is the wide range of rates of stimulus presentation that have been employed. The first two studies examined this issue. The third study was designed to directly compare N1 and wNd.

Summary of Findings

Changes in the P1-N1-P2 complex during sleep onset have generally been examined by employing slow rates of stimulus presentation (at least a 1000 ms ISI). Large differences in ERP activity are usually not observed until Stage 2 of sleep. N1 may only be slightly attenuated in Stage 1 of sleep, perhaps because of the intrusive effects of stimuli presented at a slow rate. Thus, in Experiment 1, tones were presented to subjects at a rapid rate (every 600 ms). Subjects were not required to respond to the stimulus presentations. During the Alert Wakefulness

condition a large, fronto-central P1-N1-P2 complex was observed. The N1 response inverted in polarity at the mastoid. During Stage 2 sleep, N1 amplitude was near baseline level. During Stage 1, N1 was near baseline level and was only marginally larger than during Stage 2 sleep. The monotony associated with the rapid rate of stimulus presentation may have prevented the periodic arousals that can occur when stimuli are presented at slower rates. Stimuli presented slowly are more intrusive than those that are presented more rapidly. An alternative explanation was that the early changes in the P1-N1-P2 vertex complex (occurring between Relaxed Wakefulness and Stage 1 of sleep) were a result of subjects not having been engaged in a behavioural response task - a requirement in some previous studies.

In addition to a decrease in the amplitude of N1, a concomitant increase in the amplitude of both P1 and P2 potentials was noted during the sleep onset period. There were no peak-to-peak (P1-N1 and N1-P2) amplitude differences among conditions. Sleep onset was therefore associated with the removal of an overlapping negative slow wave, the wNd wave, from the P1-N1-P2 complex.

A late N2 was also measured. Again, there is much controversy in the literature about N2. Some labs indicate it increases in amplitude while others do not. In Experiment 1, this potential did not increase in amplitude and, if anything, showed a decrease as subjects moved into definitive Stage 2 sleep. This is in contrast to results from most other studies (Ornitz et al.,

1967; Ogilvie et al., 1991; Harsh et al., 1994). The inclusion of either vertex sharp waves or K-Complexes in the averaged waveform may have resulted in the increased N2 amplitude noted in previous studies.

The results of Experiment 1, therefore, were in contrast to those of most other studies. This was due to either (a) the rapid rate of stimulus presentation, or (b) the absence of a requirement for an overt response. In previous studies stimuli were presented relatively slowly. Moreover, in some of these studies, subjects were required to overtly respond to the stimuli while in other studies, they were not. The results of Experiment 1 found ERP differences occurred early in the sleep onset period. Were the results due to the speeded rate of stimulus presentation or because no behavioural response was required? Experiment 2 was designed to answer this question. Stimuli were presented at a relatively slow rate (every 1000 ms) compared to Experiment 1 but again, subjects were not required to make a behavioural response. During the Alert Wakefulness condition, a clear N1 response was evident which inverted in polarity at the mastoid. During Stage 2 sleep the N1 response again decreased to near baseline levels. These results were thus essentially identical to those observed in Experiment 1. In contrast to the results of Experiment 1, however, N1 was still well above baseline level during Stage 1 sleep. These results replicate the findings of most previous studies, some of which required subjects to behaviourally respond to the eliciting stimuli, and others which required no overt

behavioural response.

In addition to a decrease in the amplitude of the N1 ERP, again a concomitant increase in the amplitude of both P1 and P2 ERPs was noted. Thus, sleep onset appeared to be associated with the removal of an overlapping negative slow wave, the wNd wave, from the P1-N1-P2 complex. The gradual removal of this wNd wave (also observed in Experiment 1) appeared to correspond with the progressive reduction in arousal and/or attention (consciousness) associated with the onset of sleep.

Although not significant, a trend toward an augmented sleep N2 wave was found as subjects moved into definitive sleep. The rate of stimulus presentation, therefore, also appears to interact with the amplitude of N2. Slower rates of stimulus presentation correspond to an augmentation of this late negativity.

The major ERP laboratories around the world (Hillyard-San Diego; Näätänen-Finland; Giard-Lyon) appear to concur that N1 and Nd are independent processes. This is because N1 and Nd can be manipulated independently. The first two studies of this thesis provide strong evidence that this is, in fact, not the case. N1 appeared to be almost entirely endogenous. A second line of support for the notion that N1 and Nd are independent comes from scalp distribution studies. N1 and Nd have different distributions. Their intra-cranial generators must also be different. Of course, this line of reasoning assumes that the N1 recorded in Ignore conditions is solely reflective of exogenous

processes. Experiments 1 and 2 demonstrated the flaw in this argument. Experiment 3 was designed to test the second line of evidence - the independence of N1 and Nd intra-cranial generators. To do so required that the EEG be recorded from many more channels. Spatial resolution, therefore, was enhanced by recording from 29 scalp electrode sites. Several additional, novel methodological changes were made in this final study. Stimuli were presented to subjects in an oddball paradigm (with a relatively long 1500 ms ISI). Subjects were required to press a hand held button whenever they detected a target stimulus. Thus, evidence of consciousness of the stimulus could be determined by four different measures including the characteristics of the EEG, the accuracy of subjects' behavioural detection of the target stimuli, the amplitude of the N1 to the frequently occurring stimuli, and by the presence of a P3 response to the target stimuli.

Behavioural reaction time slowed as subjects became drowsy and finally entered definitive sleep. Almost all target tones were detected during Wakefulness, while almost none were detected during Stage 2 sleep. About 50% were detected during Stage 1 sleep. During Wakefulness, a clear N1 response was evident, which inverted in polarity at the mastoid. During Stage 2 sleep, as in the previous two experiments, N1 decreased to near baseline levels. N1 was again attenuated but above baseline during Stage 1 of sleep. Again, the wNd wave was gradually removed during the sleep onset period similar to that observed in Experiments 1 and

2. The scalp distribution maps of N1b (the vertex component of the N1 complex) and wNd waves were very similar. In addition, current source density maps of the N1 and wNd waves were quite similar. There was thus, no evidence of independent and different intra-cranial generators for N1 and wNd. In contrast to the Näätänen-Hillyard-Giard assumption, N1 is not exogenous. It is almost entirely endogenous.

The sleep N2 wave was found to increase in amplitude as subjects moved into definitive Stage 2 sleep, again confirming previous findings (Ornitz et al., 1967; Ogilvie et al., 1991; Harsh et al., 1994). The scalp distribution of the waking and sleeping N2s were quite different. This suggests they are most likely different components, reflecting different intra-cranial processes.

A late positive P3 response was also observed in response to the rare, target stimuli presented during Wakefulness and Stage 1 sleep. This wave was largest during the Wakefulness condition and remained large to the detected targets during Stage 1 sleep, disappearing to near baseline levels during Stage 2 of sleep. A partial P3 response was also observed to the missed targets in Stage 1 sleep. The scalp distribution of the P3 to detected target tones in Wakefulness and to both detected and missed targets in Stage 1 sleep were all very similar. Thus, in both Wakefulness and Stage 1 sleep, subjects appear to be conscious of the target stimuli. The decrease in subject's P3 response in Stage 2 of sleep was parallelled by the decrease observed in the

amplitude of the N1 and subjects' reduced behavioural response to the target stimuli.

The data presented in this thesis indicate that the N1 component of the auditory evoked potential can potentially reflect an accurate measurement of a subject's conscious awareness of the external stimulus. As such, N1 may provide a convenient and easy means to monitor the level of attention/consciousness in a number of applied settings. These might include assessing the degree of subject's awareness during surgical operations, assessing the sedating effects of new medications, and the quantification of subject's attentiveness to aid in the clinical diagnoses of illnesses such as Attention Deficit Disorder, Bi-Polar Depression and Schizophrenia to name a few.

Novel Findings and Claims

A number of novel findings were made in the course of this thesis:

1. During definitive sleep (Stage 2 in all three experiments, and when subjects fail to respond as in study 3), N1 is at or below baseline level. Since the physical stimulus did not change between the waking and sleeping states, the attenuation of N1 must be due to endogenous processes such as a variation in the subjects' level of attention or arousal.

2. A radical and novel interpretation of this data is that N1 is entirely endogenous in nature. Variation in N1 amplitude, for whatever reason, appears to be due to the extent of the subjects' conscious awareness of the stimulus. It has been generally accepted that N1 reflects the processing of the physical stimulus, and Nd the additional processing that an attended channel receives. This thesis indicates that this notion is wrong.

3. Both N1b and wNd waves have similar scalp topographies. There is no evidence that the two waveforms have different intra-cranial processes.

4. The rate of stimulus presentation does affect the point of time when N1 is attenuated to baseline level. With a rapid rate of presentation, this occurs in Stage 1 of sleep. With a slow rate of presentation, it does not occur until Stage 2.

5. The N2 wave observed during sleep is probably a different wave than that observed during wakefulness. The scalp topography of the sleep N2 is quite distinctive from the N2 recorded during wakefulness.

6. Overt, conscious responses to target stimuli were rare in Stage 2 of sleep. Misses were rare during the Waking state. In Stage 1 of sleep, target detection occurred on about 50% of trials. From this perspective, definitive sleep (lack of consciousness) does not occur until Stage 2 of sleep although it may begin to occur in Stage 1.

7. P3 was apparent to detected targets in both the Waking state and in Stage 1 of sleep. It was not apparent in Stage 2. Again, from this perspective, definitive sleep occurs in Stage 2. P3 was also apparent, although attenuated, to undetected targets in Stage 1. From a behavioural perspective, subjects provided no evidence of conscious awareness. From the physiological perspective, there was evidence of consciousness.

8. During Stage 2, both the behavioural performance (the failure to make overt detections) and the physiological indices (the consistent absence of N1 in all three experiments and the absence of P3 in the third experiment) provide strong evidence that subjects are unconscious. During Stage 1, the evidence is much more equivocal. Subjects may or may not make overt detections. When they do, RT is delayed. P3 is large to detected targets but is still apparent when they are not overtly detected. N1 may be at baseline level (if stimuli are presented rapidly) or at an intermediate level (if stimuli are presented slowly). It is thus possible that consciousness may wax and wane in stage 1. It may be on a continuum from full consciousness at one extreme to a complete lack of consciousness at the other extreme interspersed with periods of partial (or "fuzzy") consciousness.

9. When does sleep occur? Certainly during Stage 2, but at times even in Stage 1.

REFERENCES

Aguirre, M. and Broughton, R.J. Complex event-related potentials (P300 and CNV) and MSLT in the assessment of excessive daytime sleepiness in narcolepsy-cataplexy. Electroencephalography and Clinical Neurophysiology, 1987, 67: 298-316.

Alcaini, M., Giard, M.H., Thévenet, M. and Pernier, J. Two separate frontal components in the N1 wave of the human auditory evoked response. Psychophysiology, 1994, 31: 611-615.

Alho, K., Paavilainen, P., Reinikainen, K., Sams, M. and Näätänen, R. Separability of different negative components of the event-related potential associated with the auditory stimulus processing. Psychophysiology, 1986, 23: 613-623.

Amadeo, M. and Shagass, C. Brief latency click-evoked potentials during waking and sleep in man. Psychophysiology, 1973, 10: 244-250.

Armitage, R., Bell, I., Campbell, K. and Stelmack, R. Asymmetrical auditory probe evoked potentials during REM and NREM sleep. Sleep, 1990, 13: 69-78.

Arezzo, J., Pickoff, A. and Vaughan, H.G. The sources and intracerebral distribution of auditory evoked potentials in the alert rhesus monkey. Brain Research, 1975, 90: 57-73.

Bartoli, E. and Campbell, K. The effects of stimulus intensity and rate of presentation on the evoked K-complex during sleep. 4th International Congress of Sleep Research Abstracts. Bologna, Italy, 1988, 33.

Bastien, C. and Campbell, K. The evoked K-complex: All-or-none phenomenon? Sleep, 1992, 15: 236-245.

Bastien, C. and Campbell, K. Effects of rate of tone-pip stimulation on the evoked K-complex. Journal of Sleep Research, 1994, 3: 65-72.

Bastuji, H., García-Larrea, L., Bertrand, O and Mauguière, F. BAEP latency changes during nocturnal sleep are not correlated with sleep stages but with body temperature variations. Electroencephalography and Clinical Neurophysiology, 1988, 70: 9-15.

Bastuji, H., García-Larrea, L., Franc, C. and Mauguière, F. Sleep-related modifications of auditory cognitive potentials. A topographic study during physiological all night sleep. In: Abstracts of the 10th Congress of the European Sleep Society, 1990: 379.

Bastuji, H., García-Larrea, L., Franc, C. and Mauguière, F. Brain processing of stimulus deviance during slow-wave and paradoxical sleep: A study of human auditory evoked responses using the oddball paradigm. Journal of Clinical Neurophysiology, 1995, 12: 155-167.

Baule, G. and McFee, R. Theory of magnetic detection of the heart's electrical activity. Journal of Applied Physiology, 1965, 36: 2066-2073.

Beagley, H.A. and Knight, J.J. Changes in auditory evoked response with intensity. Journal of Laryngology and Otology, 1967, 81: 881-873.

Bertrand, O., Perrin, F. and Pernier, J. A theoretical justification of the average reference in topographic evoked potential studies. Electroencephalography and Clinical Neurophysiology, 1985, 62: 462-464.

Bertrand, O., Perrin, F. and Pernier, J. Evidence for a tonotopic organization of the auditory cortex observed with auditory evoked potentials. Acta Otology-Laryngology, 1991, Supplement 491: 116-123.

Blom, J.L. and Anneveldt, M. An electrode cap tested. Electroencephalography and Clinical Neurophysiology, 1982, 54: 591-594.

BMDP Statistical Software. University of California Press, Berkeley, California, 1988.

Broadbent, D.E. Perception and Communication. New York: Pergammon, 1958.

Broadbent, D.E. Stimulus set and response set: Two kinds of selective attention. In: D.I. Mostofsky (Ed.), Attention: Contemporary Theory and Analysis. New York: Appleton-Century-Crofts, 1970.

Broadbent, D.E. Decision and Stress. New York: Academic Press, 1971.

Broadbent, D.E. Task combination and selective intake of information. Acta Psychology, 1982, 50: 253-290.

Broughton, R.J. Evoked Potentials and Sleepiness States in Man. Paper presented at the 9th European Congress of Sleep Research, Jerusalem, Israel, 1988.

Campbell, K.B. Mental chronometry. I. Behavioural and physiological techniques. In: B. Kirkaldy (Ed.), Individual Differences in Movement. Lancaster: MPT Press, 1985: 117-146.

Campbell, K. and Bartoli, E. Human auditory evoked potentials during natural sleep: The early components. Electroencephalography and Clinical Neurophysiology, 1986, 65: 142-149.

Campbell, K., Bell, I. and Bastien, C. Evoked potential measures of information processing during natural sleep. In: R.J. Broughton and R.D. Ogilvie (Eds.), Sleep, Arousal and Performance. Birkhauser, Boston, Cambridge, MA, 1992, 88-116.

Campbell, K.B., Courchesne, E., Picton, T.W. and Squires, K.C. Evoked potential correlates of human information processing. Biological Psychology, 1979, 8: 45-68.

Campbell, K.B., McGarry, P.A. and Bell, I. Information processing during sleep: The effects of high stimulus intensity. In: W.P. Koella, F. Obal, H. Schulz and P. Visser (Eds.), Sleep '86. Gustav Fisher Verlag, Stuttgart, Germany, 1988.

Childers, D.G., Perry, N.W. and Fischler, I.A. Event-related potentials: A critical review of methods for single trial detection. Critical Reviews in Biomedical Engineering, 1987, 14: 185-200.

Connoly, J.F., Aubry, McGillivary, N. and Scott, D.W. Human brainstem auditory evoked potentials (BAEP) fail to provide evidence of efferent modulation of auditory input during attentional tasks. Psychophysiology, 1989, 26: 292-303.

Côté, K., de Lugt, D.R. and Campbell, K.B. Topographic analysis of the auditory K-complex. Sleep Research, 1996, 25: 5.

Davis, H. Enhancement of evoked cortical potentials in humans related to a task requiring a decision. Science, 1964, 145: 182-183.

Davis, H. Principles of electric response audiometry. Annals of Otology Supplement, 1976, 28: 4-96.

Davis, H., Davis, P.A., Loomis, A.L., Harvey, E.N. and Hobart, G. Electrical reactions of the human brain to auditory stimulation during sleep. The Journal of Neurophysiology, 1939, 2: 500-514.

Davis, H., Mast, T., Yoshie, N. and Zerlin, S. The slow response of the human cortex to auditory stimuli: Recovery process. Electroencephalography and Clinical Neurophysiology, 1966, 21: 105-113.

Deacon-Elliot, D., Bell, I. and Campbell, K. Estimation of auditory threshold during sleep using brainstem auditory evoked-potentials. Audiology, 1987, 26: 363-368.

de Lugt, D.R., Loewy, D. and Campbell, K. The effect of sleep onset on event-related potentials with rapid rates of stimulus presentation. Electroencephalography and Clinical Neurophysiology, 1996, 98: 484-492.

Donald, M.W. and Little, R. The analysis of stimulus probability inside and outside the focus of attention, as reflected by the auditory N1 and P3 components. Canadian Journal of Psychology, 1981, 35: 175-187.

Donchin, E. Surprise! .. Surprise? Psychophysiology, 1981, 18: 493-513.

Donchin, E. and Coles, M.G.H. Is the P300 component a manifestation of context updating? Behavioural and Brain Sciences, 1988, 11: 357-374.

Donchin, E., Ritter, W. and McCallum, W.C. Cognitive Psychophysiology: The endogenous components of the ERP. In: E. Callaway, P. Teuting and S.H. Koslow (Eds.), Event-Related Brain Potentials in Man, New York: Academic Press, 1978.

Duncan-Johnson, C.C. and Donchin, E. On quantifying surprise: The variation of event-related potentials with subjective probability. Psychophysiology, 1977, 14: 456-467.

Elberling, C., Bak, C., Kofoed, B., Lebech, J. and Saermark, K. Magnetic auditory responses from the human brain. Scandinavian Audiology, 1980, 9: 185-190

Elberling, C., Bak, C., Kofoed, B., Lebech, J. and Saermark, K. Auditory magnetic fields from the human cortex. Scandinavian Audiology, 1981, 10: 203-207.

Erwin, R. and Buchwald, J. Midlatency auditory evoked responses: Differential effects of sleep in the human. Electroencephalography and Clinical Neurophysiology, 1986, 65: 383-392.

Fitzgerald, P.G. and Picton, T.W. Event-related potentials recorded during the discrimination of improbable stimuli. Biological Psychology, 1983, 17: 241-276.

Fruhstorfer, H. Habituation and dishabituation of the human vertex response. Electroencephalography and Clinical Neurophysiology, 1971, 30: 306-312.

Fruhstorfer, H. and Bergstöm, R.M. Human vigilance and auditory evoked responses. Electroencephalography and Clinical Neurophysiology, 1969, 27: 346-355.

Giard, M.H., Perrin, F., Echallier, J.F., Thévenet, M., Froment, J.C. and Pernier, J. Dissociation of temporal and frontal components in the human auditory N1 wave: a scalp current density and dipole model analysis. Electroencephalography and Clinical Neurophysiology, 1994, 92: 238-252.

Giard, M.H., Perrin, F., Pernier, J. and Perronet, F. Several attention-related wave forms in auditory areas: a topographical study. Electroencephalography and Clinical Neurophysiology, 1988, 69: 371-384.

Goff, G.D., Matsumiya, Y., Allison, T. and Goff, W.R. The scalp topography of human somatosensory and auditory evoked potentials. Electroencephalography and Clinical Neurophysiology, 1977, 42: 57-76.

Goff, W.R., Matsumiya, Y., Allison, T. and Goff, G.D. Cross-modality comparisons of averaged evoked potentials. In: E. Donchin and D.B. Lindsley (Eds.), Averaged Evoked Potentials, Washington, D.C.: NASA, 1969, 95-141.

Greenhouse, S.W. and Geisser, S. On methods in analysis of profile data. Psychometrika, 1959, 24: 95-112.

Hackley, S.A., Woldorff, M. and Hillyard, S.A. Combined use of microreflexes and event-related brain potentials as measures of auditory selective attention. Psychophysiology, 1987, 24: 632-647.

Hackley, S.A., Woldorff, M. and Hillyard, S.A. Cross-modal selective attentional effects on retinal, myogenic, brainstem, and cerebral evoked potentials. Psychophysiology, 1990, 27: 195-208.

Hansen, J.C. and Hillyard, S.A. Endogenous brain potentials associated with selective auditory attention. Electroencephalography and Clinical Neurophysiology, 1980, 49: 277-290.

Hansen, J.C. and Hillyard, S.A. Effects of stimulation rate and attribute cuing on event-related potentials during selective auditory attention. Psychophysiology, 1984, 21: 394-405.

Hari, R., Aittoniemi, K., Järvinen, M.L., Katila, T. and Varpula, T. Auditory evoked transient and sustained magnetic fields of the human brain. Localization of neural generators. Experimental Brain Research, 1980, 40: 237-240.

Hari, R., Kaila, K., Katila, T., Tuomisto, T. and Varpula, T. Interstimulus interval dependence of the auditory vertex response and its magnetic counterpart: Implications for their neural generation. Electroencephalography and Clinical Neurophysiology, 1982, 54: 561-569.

Harsh, J., Voss, U., Hull, J., Schrepfer, S. and Badia, P. ERP and behavioral changes during the wake/sleep transition. Psychophysiology, 1994, 31: 244-252.

Harsh, J., Voss, U., Hull, J. and Williamson, S. ERPs during the sleep/wake transition. In: Abstracts of the Tenth Congress of the European Sleep Research Society, 1990, 378.

Hartley, I.R. The effect of stimulus relevance on the cortical evoked potentials. Quarterly Journal of Experimental Psychology, 1970, 22: 531-546.

Hillyard, S.A., Hink, R.F., Schwent, V.L. and Picton, T.W. Electrical signs of selective attention in the human brain. Science, 1973, 182: 177-180.

Hirschorn, N. and Michie, P. Brainstem auditory evoked potentials (BAEPs) and selective attention revisited. Psychophysiology, 1990, 27: 494-512.

Hull, J., Harsh, J. and Badia, P. Psychological determinants of event-related potentials during the wake/sleep transition. Sleep Research, 1990, 20: 156.

James, W. The Principles of Psychology, New York: Holt, 1890.

Jewitt, D.L. and Williston, J.S. Auditory-evoked far fields averaged from the scalp of humans. Brain, 1971, 94: 681-696.

Johnson, L.C. Are stages of sleep related to waking behaviour? American Scientist, 1973, 61: 326-338.

Johnson, R. Jr. Event-related potential insights into the neurobiology of memory systems. In: R. Johnson Jr. and J.C. Baron (Eds.), Handbook of Neuropsychology, Volume 10, Section 14: Event-Related Brain Potentials and Cognition. Amsterdam: Elsevier, 1995: 135-163.

Jones, L. and Baxter, R. Changes in the auditory middle latency responses during all-night sleep recording. British Journal of Audiology, 1988, 22: 279-285.

Kaufman, L. and Williamson, S.J. Recent developments in neuromagnetism. In: C. Barber and T. Blum (Eds.), Evoked Potentials III, New York: Butterworths, 1987.

Kevanishvili, Z.S. and von Specht, H. Human slow auditory evoked potentials during natural and drug induced sleep. Electroencephalography and Clinical Neurophysiology, 1979, 47: 280-288.

Knight, R.T., Hillyard, S.A., Woods, D.L. and Neville, H.J. The effects of frontal and temporal-parietal lesions on the auditory evoked potential in man. Electroencephalography and Clinical Neurophysiology, 1980, 50: 112-124.

Kutas, M. Event-related brain potential (ERP) studies of cognition during sleep: is it more than a dream? In: R.R. Bootzin, J.F. Kihlstom and D.L. Schacter (Eds.), Sleep and Cognition. American Psychological Association, Washigton, 1990, 289-303.

Lehmann, D. and Skrandies, W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. Electroencephalography and Clinical Neurophysiology, 1980, 48: 609-621.

Linden, R., Campbell, K., Hamel, G. and Picton, T. Human auditory steady-state evoked potentials during sleep. Ear and Hearing, 1985, 6: 167-174.

Loewy, D.H., Campbell, K.B. and Bastien, C. The mismatch negativity to frequency deviant stimuli during natural sleep. Electroencephalography and Clinical Neurophysiology, 1996, 98: 493-501.

Lucas, J.H. Human auditory attention: The olivocochlear bundle may function as a peripheral filter. Psychophysiology, 1980, 17: 444-452.

Lucas, J.H. The role of efferent inhibition in human auditory attention. An examination of the auditory brainstem potentials. International Journal of Neuroscience, 1981, 12: 137-145.

McCallum, W.C. and Curry, S.H. Hemisphere differences in event-related potentials and CNVs associated with monaural stimuli and lateralized motor responses. In: D. Lehmann and E. Callaway (Eds.), Human Evoked Potentials: Applications and Problems. New York: Plennum, 1979: 232-250.

McCallum, W.C. and Curry, S.H. The form and distribution of auditory of evoked potentials and CNVs when stimuli and responses are lateralized. In: H.H. Kornhuber and L. Deecke (Eds.), Progress in Brain Research, Volume 54, Motivation, Motor and Sensory Processes of the Brain: Electrical Potentials, Behaviour and Clinical Use. Amsterdam: Elsevier, 1980: 767-775.

Möcks, J., Kohler, W., Gasser, T. and Pham, D.T. Novel approaches to the problem of latency jitter. Psychophysiology, 1988, 25: 217-226.

Näätänen, R. Selective attention and evoked potentials. Annals Academiae Scientiarum Fennicae, 1967, 151: 1-226.

Näätänen, R. Evoked potentials and selective attention in humans - a critical review. Biological Psychology, 1975, 2: 237-307.

Näätänen, R. Processing negativity: An evoked-potential reflection of selective attention. Psychological Bulletin, 1982, 92: 605-640.

Näätänen, R. The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. Behavioural and Brain Sciences, 1990, 13: 201-288.

Näätänen, R. Attention and Brain Function. Lawence Earlbaum Associates, Hillsdale, New Jersey, 1992.

Näätänen, R. and Alho, K. Event-related potentials in human selective attention research. In: R. Johnson Jr. and J.C. Baron (Eds.), Handbook of Neuropsychology, Volume 10, Section 14: Event-Related Brain Potentials and Cognition. Amsterdam: Elsevier, 1995: 75-104.

Näätänen, R., Gaillard, A.W.K. and Mäntysalo, S. Early selective-attention effect reinterpreted. Acta Psychologica, 1978, 42: 313-329.

Näätänen, R., Gaillard, A.W.K. and Varey, C.A. Attention effects on auditory EPs as a function of interstimulus interval. Biological Psychology, 1981, 13: 173-187.

Näätänen, R. and Mitchie, P.T. Early selective attention effects on the evoked potential. A critical review and reinterpretation. Biological Psychology, 1979, 8: 81-136.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K. and Sams, M. The mismatch negativity to intensity changes in auditory stimulus sequence. In: R. Johnson Jr., J.W. Rohrbaugh and R. Parasuraman (Eds.), Current Trends in Event-Related Potential Research, (suppl. 40 to Electroencephalography and Clinical Neurophysiology). Amsterdam: Elsevier, 1987a: 125-131.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K. and Sams, M. Inter-stimulus interval and the mismatch negativity In: C. Barber and T. Blum (Eds.), Evoked Potentials III. London: Butterworth, 1987b: 392-397.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K. and Sams, M. Do even-related potentials reveal the mechanism of auditory sensory memory in the human brain? Neuroscience Letters, 1989a, 98: 217-221.

Näätänen, R., Paavilainen, P. and Reinikainen, K. Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? Neuroscience Letters, 1989b, 107: 347-352.

Näätänen, R. and Picton, T. The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. Psychophysiology, 1987, 24(4): 375-425.

Näätänen, R., Sams, M. and Alho, K. The mismatch negativity: The ERP sign of a cerebral mismatch process. In: W.C. McCallum, R. Zappoli and F. Denoth (Eds.), Cerebral Psychophysiology: Studies in Event-related Potentials (suppl. 38 to Electroencephalography and Clinical Neurophysiology). Amsterdam: Elsevier, 1986: 174-180.

Näätänen, R., Simpson, M. and Loveless, N.E. Stimulus deviance and evoked potentials. Biological Psychology, 1982, 14: 53-98.

Nielsen-Bohlman, L., Knight, R.T, Woods, D.L. and Woodward, K. Differential auditory processing continues during sleep. Electroencephalography and Clinical Neurophysiology, 1991, 79: 281-290.

Noldy, N., McGarry, P. and Campbell, K. Late auditory evoked potentials as indicators of sleep onset. In: W. Koella, F. Obal, H. Schultz and P. Visser (Eds.), Sleep '86. Gustav, Fisher, Verlag, Stuttgart, Germany, 1988.

Ogilvie, R.D., Battye, R.A. and Simons, I.A. Are there changing CNS priorities in sleepiness and sleep? EEG and ERP evidence. In: R.D. Ogilvie and J.R. Harsh (Eds.), Sleep Onset: Normal and Abnormal Processes. Washington, DC: American Psychological Association, 1994: 269-288.

Ogilvie, R.D., Simons, I., Kuderian, R., MacDonald, T. and Rustenberg, J. Behavioral, event-related potential, and EEG/FFT changes at sleep onset. Psychophysiology, 1991, 28: 54-64.

Ogilvie, R.D. and Wilkinson, R.T. The detection of sleep onset: Behavioral and physiological convergence. Psychophysiology, 1984, 21: 510-520.

Ogilvie, R.D., Wilkinson, R.T. and Allison, S. The detection of sleep onset: Behavioural, physiological, and subjective convergence. Sleep, 1989, 12: 458-474.

Okita, T., Konishi, K. and Inamori, R. Attention-related negative brain potential for speech words and pure tones. Biological Psychology, 1983, 16: 29-47.

Ornitz, E.M., Ritvo, E.R., Carr, E.M., La Franchi, S. and Walter, R.D. The effect of sleep onset on the auditory averaged evoked response. Electroencephalography and Clinical Neurophysiology, 1967, 23: 335-341.

Osterhammel, P., Shallop, J. and Terkildsen, K. The effect of sleep on the auditory brainstem response (ABR) and the middle latency response (MLR). Scandinavian Audiology, 1985, 14: 47-50.

Oswald, I., Taylor, A.M. and Treisman, M. Discriminative responses to stimulation during human sleep. Brain, 1960, 83: 440-453.

Paavilainen, P., Alho, K., Reinikainen, K., Sams, M. and Näätänen, R. Right hemisphere dominance of different mismatch negativities. Electroencephalography and Clinical Neurophysiology, 1991, 78: 466-479.

Paavilainen, P., Cammann, R., Alho, K., Reinikainen, K., Sams, M. and Näätänen, R. Event-related potentials to pitch change in a repetitive auditory sequence during sleep. In: R. Johnson Jr., J. Rohrbaugh and R. Parasuraman (Eds.), Current Trends in Event-Related Potential Research, (suppl. 40 to Electroencephalography and Clinical Neurophysiology). Amsterdam: Elsevier, 1987, 246-255.

Pernier, J., Perrin, F. and Bertrand, O. Scalp current density fields: Concepts and properties. Electroencephalography and Clinical Neurophysiology, 1988, 69: 385-389.

Perrault, N. and Picton, T.W. Event-related potentials recorded from the scalp and nasopharynx. I. N1 and P2. Electroencephalography and Clinical Neurophysiology, 1984, 59: 177-194.

Perrin, F., Bertrand, O. and Pernier, J. Scalp current density mapping: Value and estimation from potential data. IEEE Trans Biological Engineering, 1987, 34: 283-288.

Perrin, F., Pernier, J., Bertrand, O. and Echallier, J.F. Spherical splines for scalp potential and current density mapping. Electroencephalography and Clinical Neurophysiology, 1989, 72: 184-187.

Perrino, A. and Campbell, K. The P50 during wakefulness and sleep: The effects of stimulus parameters and filter bandpass. Psychophysiology. 1996, 33 (suppl. 1): 68.

Picton, T.W. The P300 wave of the human event-related potential. Journal of Clinical Neurophysiology, 1992, 9: 456-479.

Picton, T.W., Campbell, K.B., Baribeau-Braun, J. and Proulx, G.B. The neurophysiology of human attention. A tutorial review. In: J. Requin (Ed.), Attention and Performance VII, New York: Erlbaum, 1978.

Picton, T.W. and Hillyard, S.A. Human auditory evoked-potentials. II. Effects of attention. Electroencephalography and Clinical Neurophysiology, 1974, 36: 191-200.

Picton, T.W. and Hillyard, S.A. Endogenous event-related potentials. In T.W. Picton (Ed.), Human Event-Related Potentials: Volume 3. EEG Handbook, New York: Elsevier, 1988, 361-426.

Picton, T.W., Hillyard, S.A., Krausz, H.I. and Galambos, R. Human auditory evoked potentials. I. Evaluation of components. Electroencephalography and Clinical Neurophysiology, 1974, 36: 179-190.

Picton, T.W. and Hink, R,F. Evoked potentials: How? What? and Why? American Journal of EEG Technology, 1974, 14: 9-44.

Picton, T.W., Hink, R.F., Perez-Abalo, M., Linden, R.D. and Wiens, A.S. Evoked potentials: How now? Journal of Electrophysiology and Technology, 1984, 10: 177-221.

Picton, T.W., Lins, O.G. and Scherg, M. The recording and analysis of event-related potentials. In: R. Johnson Jr. and J.C. Baron (Eds.), Handbook of Neuropsychology, Volume 10. Amsterdam: Elsevier, 1995: 3-74.

Picton, T.W., Stapells, D.R. and Campbell, K.B. Auditory evoked potentials from the human cochlea and brainstem. Journal of Otolaryngology, 1981, 10: 1-41.

Picton, T.W. and Stuss, D.T. The component structure of the human event-related potentials. In: H.H. Kornhuber and L. Deecke (Eds.), Progress in Brain Research, Volume 54, Motivation, Motor and Sensory Processes of the Brain: Electrical Potentials, Behaviour and Clinical Use. Amsterdam: Elsevier, 1980, 17-49.

Picton, T.W., Woods, D.L., Baribeau-Braun, J. and Healey, T.M.G. Evoked potential audiometry. Journal of Otolaryngology, 1977, 6: 90-119.

Plourde, G. and Picton, T.W. Long-latency auditory evoked potentials during general anesthesia: N1 and P3 components. Anesthesia and Analgesia, 1991, 72: 342-350.

Pritchard, W.S. Psychophysiology of P300. Psychological Bulletin, 1981, 89: 506-540.

Rechtschaffen, A. and Kales, A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Brain Information Service/Brain Research Institute, Los Angeles, UCLA, 1968.

Richer, F., Alain, C., Achim, A., Bouvier, G. and Saint-Hilaire, J.M. Intracerebral amplitude distributions of the auditory evoked potential. Electroencephalography and Clinical Neurophysiology, 1989, 74: 202-208.

Ritter, W. and Vaughan, H.G. Average evoked responses in vigilance and discrimination: A reassessment. Science, 1969, 164: 326-328.

Ruchkin, D.S., Johnson, R., Canoune, H.L., Ritter, W. and Hammer, M. Multiple sources of P3b associated with different types of information. Psychophysiology, 1990, 27: 157-176.

Salisbury, D., Squires, N.K., Ibel, S. and Maloney, T. Auditory event-related potentials during Stage 2 NREM sleep in humans. Journal of Sleep Research, 1992, 1: 251-257.

Scherg, M. and Picton, T. Separation and identification of event-related potential components by brain electric source analysis. In: C.H.M. Brunia, G. Mulder and M.N. Verbaten (Eds.), Event-Related Brain Research. Electroencephalography and Clinical Neurophysiologgy, Suppliment 42. Amsterdam: Elsevier, 1991: 24-37.

Scherg, M., Vajsar, J. and Picton, T.W. A source analysis of the late auditory evoked potentials. Journal of Cognitive Neuroscience, 1989, 1: 336-355.

Scherg, M. and Von Cramon, D. Two bilateral sources of the late EP as identified by a spatio-temporal dipole model. Electroencephalography and Clinical Neurophysiology, 1985, 62: 32-44.

Scherg, M. and Von Cramon, D. Evoked dipole source potentials of the human auditory cortex. Electroencephalography and Clinical Neurophysiology, 1986a, 65: 344-360.

Scherg, M. and Von Cramon, D. Psychoacoustic and electrophysiological correlates of central hearing disorders in man. European Archives of Psychiatric Neurological Sciences, 1986b, 236: 56-60.

Scherg, M. and Von Cramon, D. Dipole source potentials of the auditory cortex in normal subjects and in patients with temporal lobe lesions. In: F. Grandori, M. Hoke and G. Romani (Eds.), Auditory Evoked Magnetic Fields and Electrical Potentials. Advances in Audiology, Basel: Karger, 1990, 165-193.

Schwent, V., Hillyard, S.A. and Galambos, R. Selective attention and the auditory vertex potential, I: Effects of stimulus delivery rate. Electroencephalography and Clinical Neurophysiology, 1976a, 40: 604-614.

Schwent, V., Hillyard, S.A. and Galambos, R. Selective attention and the auditory vertex potential, II: Effects of stimulus intensity and masking noise. Electroencephalography and Clinical Neurophysiology, 1976b, 40: 615-622.

Skinner, B.F. The steep and thorny way to a science of behaviour. In: R. Harre (Ed.), Problems of Scientific Revolution, Oxford: Oxford University Press, 1975.

Spong, P., Haider, M. and Lindsley, D.B. Selective attentiveness and cortical evoked responses to visual and auditory stimuli. Science, 1965, 148: 395-397.

Squires, K.C., Hillyard, S.A. and Lindsay, P.H. Vertex potentials evoked during auditory signal detection: Relation to decision criteria. Perception and Psychophysics, 1973, 14: 265-272.

Squires, K.C., Squires, N.K. and Hillyard, S.A. Decision-related cortical potentials during an auditory signal detection task with cued observation intervals. Journal of Experimental Psychology: Human Perception and Performance, 1975a, 1: 268-279.

Squires, N.K., Squires, K.C. and Hillyard, S.A. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalography and Clinical Neurophysiology, 1975b, 38: 387-401.

Statistica, StatSoft, Incorporated. Tulsa, OK, 1995.

Stelmack, R.M., Campbell, K.B. and Bell, I. Extraversion and brainstem auditory evoked potentials during sleep and wakefulness. Personality and Individual Differences, 1993, 14: 447-453.

Sutton, S., Braren, M., Zubin, J. and John, E.R. Evoked potential correlates of stimulus uncertainty. Science, 1965, 150: 1187-1188.

Teder, W., Alho, K., Reinikainen, K. and Näätänen, R. Interstimulus interval and the selective-attention effect on auditory ERPs: "N1 enhancement" versus processing negativity. Psychophysiology, 1993, 30: 71-81.

Treisman, A.M. Selective attention in man. British Medical Bulletin, 1964, 20: 12-16.

Tukey, J.W. One degree of freedom for nonadditivity. Biometrics, 1949, 5: 232-242.

Ujszászi, J. and Halász, P. Late component variants of single auditory evoked responses during NREM sleep stage 2 in man. Electroencephalography and Clinical Neurophysiology, 1986, 64: 260-268.

van Hooff, J.C., de Beer, N.A.M., Brunia, C.H.M., Cluitmans, P.J.M., Korsten, H.H.M., Tavilla, G. and Grouls, R. Information processing during cardiac surgery: An event-related potential study. Electroencephalography and Clinical Neurophysiology, 1995, 96: 433-452.

Vaughan, H.G. Jr. and Arezzo, J.C. The neural basis of event-related potentials. In: T.W. Picton (Ed.), Human event-related potentials. Handbook of Electroencephalography and Clinical Neurophysiology. Revised Series, Amsterdam: Elsevier, 1988, 45-96.

Vaughan, H.G., Jr. and Ritter, W. The sources of auditory evoked responses recorded from the human scalp. Electroencephalography and Clinical Neurophysiology, 1970, 28: 360-367.

Vaughan, H.G., Jr., Ritter, W. and Simson, R. Topographic analysis of auditory event-related potentials. In: H.H. Kornhuber and L. Deecke (Eds.), Progress in Brain Research: Vol. 54. Motivation, Motor and Sensory Processes of the Brain: Electrical Potentials, Behaviour and Clinical Use. 1980, Elsevier, Amsterdam, 279-290.

Velasco, M. and Velasco, F. Subcortical correlates of the somatic, auditory and visual vertex activities. II. Referential EEG responses. Electroencephalography and Clinical Neurophysiology, 1986, 63: 62-67.

Velasco, M., Velasco, F. and Olvera, A. Subcortical correlates of the somatic, auditory and visual vertex activities in man. I. Bipolar EEG responses and electrical stimulation. Electroencephalography and Clinical Neurophysiology, 1985, 61: 519-529.

Verbaten, M.N. Näätänen's auditory model from a visual perspective. Behavioural and Brain Sciences, 1990, 13: 256-257.

Verleger, R. A critique of the context updating hypothesis and an alternative interpretation of P3. Behavioural and Brain Sciences, 1988, 11: 343-427.

Walter, W.G., Cooper, R., Aldridge, V.J., McCallum, W.C. and Winter, A.L. Contingent negative variations: An electric sign of sensorimotor association and expectancy in the human brain. Nature, 1964, 203: 380-384.

Watson, J.B. Psychology as the behaviourist views it. Psychological Review, 1913, 20: 158-177.

Weitzman, E.D. and Kremen, H. Auditory evoked responses during different stages of sleep in man. Electroencephalography and Clinical Neurophysiology, 1965, 18: 65-67.

Wesensten, N.J. and Badia, P. The P300 component in sleep. Physiology and Behaviour, 1988, 44: 215-220.

Wilkinson, R.T. and Lee, M.V. Auditory evoked potentials and selective attention. Electroencephalography and Clinical Neurophysiology, 1972, 33: 411-418.

Wilkinson, R.T. and Morlock, H.C. Auditory evoked response and reaction time. Electroencephalography and Clinical Neurophysiology, 1966, 23: 50-56.

Williams, H.L., Morlock, H.C., Morlock, J.V. and Lubin, A. Auditory evoked responses and the EEG stages of sleep. Annals of the New York Academy of Sciences, 1964, 112: 172-179.

Williams, H.L. Tepas, D.I. and Morlock, H.C. Evoked responses to clicks and electroencephalographic stages of sleep in man. Science, 1962, 138: 685-686.

Winter, O., Kok, A., Kenemans, J.L. and Elton, M. Auditory event-related potentials to deviant stimuli during drowsiness and stage 2 sleep. Electroencephalography and Clinical Neurophysiology, 1995, 96: 398-412.

Woestenburg, J.C., Das-Smaal, E.A., Brand, E. and Kramer, S. Learning during visual search in children with attentional and learning problems, a trial to trial evaluation of RT and ERP measures. Journal of Psychophysiology, 1992, 6: 204-224.

Woldorff, M., Hansen, J.C. and Hillyard, S.A. Evidence for effects of selective attention in the mid-latency range of the human auditory event-related brain potential. In: R. Johnson Jr., J.W. Rohrbaugh and R. Parasuraman (Eds.), Current Trends in Event-Related Brain Potential Research (EEG Supplement 40). Elsevier, Amsterdam, 1987.

Woldorff, M.G. and Hillyard, S.A. Modulation of early auditory processing during selective listening to rapidly presented tones. Electroencephalography and Clinical Neurophysiology, 1991, 79: 170-191.

Wolpaw, J.R. and Penry, J.K. A temporal component of the auditory evoked response. Electroencephalography and Clinical Neurophysiology, 1975, 39: 609-620.

Wolpaw, J.R. and Wood, C.C. Scalp distribution of human auditory evoked potentials. I. Evaluation of reference electrode sites. Electroencephalography and Clinical Neurophysiology, 1982, 54: 15-24.

Wood, C.C. and Wolpaw, J.R. Scalp distribution of human auditory evoked potentials. II. Evidence for mutiple sources and involvement of auditory cortex. Electroencephalography and Clinical Neurophysiology, 1982, 54: 25-38.

Woods, D.L. and Clayworth, C.C. Scalp topographies dissociate N1 and Nd components during auditory selective attention. In: R. Johnson Jr., J.W. Rohrbaugh and R. Parasuraman (Eds.), Current Trends in Event-Related Brain Potential Research, EEG Supplement 40. Amsterdam: Elsevier, 1987.