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Evidence that the Human Auditory System Learns Rules Without Conscious Awareness

by

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Abstract

The focused sense of self that is central to our experience of consciousness could not exist without human brain's ability to process large amounts of information outside of conscious awareness. The Mismatch Negativity (MMN) is thought to index one such pre-conscious mechanism, a complex novelty detector that compares incoming sounds to rules that it has extracted from the recent acoustic past. Processes that do not require conscious awareness are considered to be "automatic". The automaticity of the MMN, however, has predominantly been studied using very simple stimuli. The present dissertation studied the issue of automaticity using a two-tone alternating pattern (e.g., ABABABAB...) as the "standard" stimuli. MMN-eliciting deviants were rule-violating tone repetitions (e.g., ABABA$\underline{\text{A}}$AB...). Three studies took complementary approaches to the problem of automaticity. Study 1 tested the automaticity of the detection of rule violations by varying the presumed attentional demands of a visual task, while the auditory pattern was ignored. The MMN was unaffected by visual task difficulty, but it may be impossible for awake, alert subjects to ever fully ignore incoming sounds. Study 2, therefore, studied the MMN during natural sleep, the period of time when the observer is least conscious of the external environment. An MMN was elicited in both the waking state and REM sleep. Interpreted in isolation, these studies might be taken as evidence that the MMN is strongly automatic. Some attention effects, however, have been reported. One proposed mechanism for these attention effects is that attention increases the strength of the memory for the frequently-presented, standard stimuli. Study 3 examined whether the MMN varies with the strength of the memory for the standard by manipulating the number of memory-reinforcing repetitions of the standard that occurred between successive deviants. The results of Study 3 suggest that the amplitude of the MMN is unrelated to the strength of the memory for the standard. Altogether, the results of these studies suggest that even complex, rule-based MMN elicitation is an automatic process, and that studies demonstrating evidence to the contrary should be examined for the influence of other confounding factors.

Acknowledgements and Dedication

No body of work of the magnitude of a doctoral dissertation can come to fruition by the efforts of one person alone. The contributions of numerous individuals, collaborators and mentors alike, must be acknowledged. To those who have worked alongside me as my supervisors, collaborators, and friends, many of whose names sit beside my own on the publications that have resulted, I offer my sincere thanks. Without your commitment, support, and advice, I would not be where I am today. I truly hope that the work that has resulted from our time together will be an enduring source of pride for you all. I'm sure they will be for me.

This dissertation, however, is dedicated to the unsung heroes of my studies: the friends and family who have travelled this road with me, and have so long endured being a second priority. Their grace, kindness, and seemingly inexhaustible compassion are a testament to the power of love, and the beauty of the human spirit. Among these, I must especially dedicate this work to my mother. Without her selflessness and personal sacrifice, none of this would have been possible, and I am blessed to have her.

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A Note on Formatting:

This dissertation is presented in article format. Therefore, those studies that have already been published in scientific journals (Study 1: Sculthorpe, Collin & Campbell, 2008 and Study 2: Sculthorpe, Ouellet & Campbell, 2009) are formatted and organized according to the specifications of the journal in which they were published, Brain Research. Consequently, the Methods section is the last section in both of these articles. As the primary investigator, and main author of each study, L. Sculthorpe is listed as the first author on these publications. Other parts of the thesis, including the General Introduction, Study 3, the Summary & Conclusions, and the Reference section follow the formatting guidelines of the American Psychological Association.

... because our senses sometimes deceive us, I would suppose that there was nothing which was such as they represented it to us. And because there are men who mistake themselves in reasoning ... I rejected as false all those reasons, which I had before taken for demonstrations. And considering, that the same thoughts which we have waking, may also happen to us sleeping ... I resolved to feign that all those things which ever entered into my mind were no more true than the illusions of my dreams. But presently after I observed that whilst I would think that all was false, it must necessarily follow that I who thought it must *be* something.

René Descartes, A Discourse on Method, p.51
1649

Chapter 1:

General Introduction

Cogito ergo sum – I think, therefore I am – are the famous words imprinted on history by René Descartes in his *Discourse on Method.* Having observed that "knowledge" was often built more on opinion than truth, Descartes sought to reject as false all ideas that could be doubted. In so doing, he found himself distrusting even the evidence presented by his own senses. Yet as he progressed, rejecting all knowledge as false, and searching for one piece of truth upon which to build his method, Descartes found the one thing that he could not escape was the existence of his own thoughts. Physical evidence could be doubted, but his ability to doubt was a certainty. Thus, Descartes' first truth was his ability to think: in other words, his own consciousness.

While the exact definition of consciousness remains a matter of considerable and long philosophical debate that is beyond the scope of this introduction, at its most basic level, consciousness relies on the experience of a continuity of thoughts and experiences in time. Almost all cognitive scientists agree that the human capacity for conscious information processing has its limits, and as such, continuity of thought and experience requires the rejection of irrelevant sensations. The observer must choose what is relevant and what is irrelevant to process. This capacity for voluntary control over access of input to conscious processing is known as selective attention. Without the ability to selectively reject sensations that are irrelevant to the current task, every stimulus in the environment would be actively processed. Existence would be a wild, ever-shifting kaleidoscope of sensations, devoid of continuity or meaning. It is unlikely that any thinking, or any consciousness, could emerge at all.

Yet unyielding focused attention, which would effectively disconnect an organism from its environment, is just as undesirable as unrestrained sensation. Success and survival rely on an organism's ability to be responsive to biologically relevant events when they lie outside the current focus of attention, whether these events are the warning signs of a predator, the sounds of a prey, the cries of its unprotected young, or the allure of a potential mate. The compromise between total sensory receptiveness and absolute focused attention is one of the major roles of the brain's pre-conscious systems, which are capable of processing a large amount of information in a relatively automatic, effortless way, prior to the time of awareness that a stimulus has indeed been presented. Without the ability to process large amounts of information at a pre-conscious level, thus preserving the continuity of conscious thought, consciousness as we know it likely could not exist.

This thesis explores the brain's pre-conscious mechanisms for processing stimuli in the auditory modality. The research is carried out under the framework of Risto Näätänen's model of attention, auditory information processing and the auditory "experience." Näätänen's is not the only model of auditory processing that has been proposed. What is unique about Näätänen's model is that it provides a means of quantifying the extent of processing of unattended stimulus input even when the observer is not aware that is has been presented. The model is built on evidence obtained through the monitoring of event-related potentials (ERPs). Auditory ERPs are minute changes in the ongoing electrical activity of the brain (the EEG) that reflect stages of information processing from levels as early as the auditory nerve to as late as high-level cortical processing, where complex perceptual and cognitive operations take place. Näätänen's model describes three routes by which observers can become conscious of auditory input. One involves selective, active attention in which a central executive that controls attentional allocation chooses to direct the limited attentional resources to an auditory channel. The other two routes involve passive attention in which highly relevant, but unattended auditory stimuli may intrude into consciousness. The first route involves a mechanism known as the transient detector, which responds to transient, abrupt changes in the energy of the acoustic environment. Such changes principally include stimulus onsets and offsets. The second route involves the processing of more complex changes in the acoustic environment. The mechanism associated with this route to attention is generally known as the change detector, and its operation is reflected by the mismatch negativity (MMN) ERP.

The present thesis is principally concerned with the operation of this complex novelty detector. The MMN signals that the brain has detected that an incoming stimulus does not conform to the regularities that it has extracted from the recent acoustic past. It is intimately linked to the contents of auditory sensory memory, and as such, is a powerful tool for observing how the brain analyzes auditory stimuli in the absence of attention. For this reason, Näätänen placed very high importance on the MMN as a tool for studying the neural mechanisms of selective attention (Näätänen, 1990). Understanding the mechanisms of selective attention, and what the automaticity of the MMN tells us, however, requires a good understanding of how the central nervous system handles auditory information. This thesis, therefore, begins with a brief discussion of the auditory nervous system and the ERPs that are associated with each stage of auditory processing. Näätänen's model is then reviewed, with particular emphasis on the MMN, and the concept of automaticity. These basic concepts provide the theoretical framework for the present thesis.

1. Auditory Processing

1.1 The Auditory Nervous System

Auditory processing in the human nervous system begins with sensory transduction in the organ of Corti, the human sensory organ which is contained within a membranous duct that spans nearly the entire length of the cochlea. The organ of Corti is innervated by the afferent and efferent fibres of the auditory nerve. The coding of information at the level of the auditory nerve is fairly simplistic. The organ of Corti and the auditory nerve are tonotopically organized, meaning that regions of the organ of Corti, and the fibres of the auditory nerve that innervate those regions, have characteristic frequencies to which they are maximally sensitive (Hudspeth, 2000). In addition to this "place code", the tonal frequency of sound is conveyed by a "frequency code" in which the fibres of the auditory nerve fire in a periodic manner that matches the frequency of incoming stimulation (Hudspeth, 1989). Fibres of the auditory nerve are also ampliotopic in their organization: each fibre responds only to sounds within a restricted intensity range (Hudspeth, 2000).

The auditory nerve maintains tonotopic organization in all of its divisions as it branches to reach the initial auditory relay station of the central nervous system, the cochlear nucleus (CN), in the medulla. In general, the function of the CN is to take the input from the cochlear nerve, which uses only a simple neural code, and tease apart relevant types of information for use by higher brainstem structures (Rhode, 1991). The 3 subdivisions of the CN contribute, largely contralaterally, to the lateral lemniscus, the major ascending auditory pathway of the brainstem, which eventually terminates in the thalamus. Two subdivisions also project extensive bilateral connections to the nuclei of the superior olivary complex (SOC), which extends from the rostral medulla to the mid-pons region.

The process of binaural hearing begins in the SOC. The SOC is made up of a number of small nuclei. The 3 major nuclei of the SOC all display tonotopy. The SOC performs binaural integration of differences in the time of arrival, phase, and intensity of sounds between the two ears for the purpose of sound localization on the horizontal plane (Carr & Konishi, 1988;

Boudreau & Tsuchitani, 1968). The nuclei of the SOC project bilaterally and ipsilaterally through the lateral lemniscus to the inferior colliculus (IC). The IC is located in the dorsal midbrain and performs a number of complex functions in the auditory system. The IC may be critical for selective attention in space (Palmer, Rees, & Caird, 1992), and may also be the point in the auditory system at which auditory information acquires timing values from an internal clock (Pedemonte, Peña, & Velluti, 1996). Fibres from the IC project to the medial geniculate body (MGB), the auditory relay centre of the thalamus. The ventral division of the MGB is the best understood, and has a lateral-to-medial tonotopic organization (Aitkin & Webster, 1971). The principal projection of the ventral MGB terminates in the primary auditory cortex. Projections from the MGB travel through the reticular nucleus of the thalamus (TRN) to reach the auditory cortex. The TRN acts as a filter that restricts information flow from the thalamus to the cortex (Guillery, Feig, & Lozsádi, 1998) and is thought to be intimately involved in attention and consciousness.

The auditory cortex, as with other sensory cortices, is typically divided into primary (AI) and non-primary (also called secondary or association) areas based on cytoarchitecture and thalamo-cortical connectivity. The human auditory cortex appears to encompass Heschl's gyrus (AI), as well as the lips of the posterior 2/3 of the Sylvian fissure, including the superior temporal gyrus and the fronto-parietal operculum (Celesia, 1976). Since there are a number of bilateral connections in the auditory brainstem, AI receives binaural information. Thus the left and right auditory cortices receive input from both ears. Maximal responses are obtained in AI by binaural stimulation: monaural stimulation causes a contralaterally maximal response (Celesia, 1976). The auditory cortices of the two hemispheres also communicate via the corpus callosum. AI is strictly tonotopically organized (Merzenich, Knight, & Roth, 1975). It has been suggested that the auditory cortex also bears an ampliotopic organization. Some fMRI data supports this concept (Bilecen, Seifritz, Scheffler, Henning, & Schulte, 2002). Five or six non-primary areas have been identified in the human temporal cortex (Rivier & Clarke, 1997; Wallace, Johnston, & Palmer, 2002). Non-primary regions receive fibres from AI, as well as from thalamic nuclei conveying polysensory information. Unlike AI, which is in many ways a cortical relay station, these regions perform higher-level analyses, and may operate in parallel (Rivier & Clarke, 1997).

1.2 Psychophysiological Measures of Auditory Information Processing

The neural activity associated with the processing of auditory stimuli can be tracked non-invasively from the cochlear nerve through the central nervous system in humans by recording ERPs at the scalp. ERPs are minute deflections that are buried in the continuous electroencephalogram (EEG). ERPs vary in amplitude from less than 1 μV to perhaps as large as 25 μV, whereas the waking EEG lies in the range of 25-100 μV. The EEG, like any electrical signal, consists of negative- and positive-going waves. Because ERPs are much smaller than the ongoing EEG, a signal averaging process is required to allow the ERP to be visualized (i.e., to improve the signal-to-noise ratio). A stimulus is presented repeatedly. The EEG is then segmented into discrete epochs (or “sweeps”) that are time-locked to an event, in most cases the onset of the stimulus. In some cases, the epochs may be time-locked to a psychological event, such as the response. These epochs are typically a few hundred milliseconds in duration. The EEG is assumed to reflect random activity (i.e., neural activity that is not tied to the processing of the repeated stimulus). It might be negative-going or it might be positive-going. The epochs are summed point-by-point, and in this process, the sum of the random negative- and positive-going “background” EEG activity that is not related to stimulus processing tends towards a zero value. The amplitude of the ERP, however, is assumed to be constant. The average of a constant value is, of course, the constant. Thus, with a sufficient number of stimulus presentations, the amplitude of random EEG should gradually become reduced, leaving the constant-amplitude ERP to emerge.

Deflections in the ERP are caused by synchronized activity in neuronal populations that are sufficiently geometrically oriented to create an "open field" dipole in which neuronal electrical activity (usually the post-synaptic potentials following dendritic stimulation) summate to produce a large enough voltage to be recorded at the scalp (Picton, Stapells, & Campbell, 1981). ERPs are usually recorded from the scalp in humans and consist of a series of negative- and positive-going "components", thought to reflect different aspects of sensory and cognitive processing of different "sources" within the brain. The scalp-recorded potential reflects the summed activity of intracerebral sources. The voltage distribution across the scalp reflects the geometric orientation of these sources and the strength of their activity.

Authors have defined independence of components in different ways. Scherg and von Cramon defined a "source potential" as "the compound local activity of a circumscribed brain region" (Scherg & von Cramon, 1986). This definition places emphasis on the independent source generators in defining an ERP component. Thus, each ERP component reflects the activity of a different intracerbral source. Donchin, Ritter, and McCallum (1978), on the other hand, stressed the role of experimental manipulations in differentiating ERP components. An experimental manipulation may affect component A, but not component B, whereas another manipulation may affect component B, but not component A (Donchin, Ritter, & McCallum, 1978). The Donchin definition places a greater role on functional independence while the Scherg and von Cramon definition depends on anatomical independence. Näätänen and Picton (1987) were influenced by both of these definitions, and defined an ERP 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" (Näätänen & Picton, 1987).

Similarly to ERPs, the magnetic component of the electromagnetic fields generated by open field neural activity can be recorded by magnetoencephalography (MEG). Signal averaging applied to the continuous MEG yields event-related fields (ERFs). ERF recording is particularly useful for source localization because the magnetic component of the electromagnetic field does not disperse when passing through tissue the same way the electric component does, making source localization more precise. Despite this precision, ERF-based localizations should be used in conjunction with ERP recordings, because ERPs and ERFs are sensitive to slightly different source generators. Only cortical sources whose dipoles are oriented tangentially (i.e., not directly perpendicular) to the scalp contribute to the MEG recording, and older MEG systems were not typically sensitive to subcortical sources (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The present work will focus on ERPs, but evidence derived from their magnetic counterparts will occasionally also be considered, particularly for source localization purposes.

Auditory ERP components can be recorded that reflect sensory, exogenous processing at the level of the auditory nerve up to higher-level cognitive, endogenous processing at the level of the cerebral cortex. Exogenous components are only affected by the physical features of the stimulus. Thus manipulation of the intensity of the stimulus would affect an exogenous component, but an endogenous manipulation, such as attention, would not. Endogenous components, on the other hand, are not affected by the physical features of the stimulus. Instead, they are sensitive to more psychological manipulations such as attention or relevance. Thus, if subjects are asked to press a button upon detection of a high-, but not a low-pitched voice, the manipulation would affect certain endogenous components, but not exogenous ones. In humans, the earliest series of exogenous auditory ERPs is a sequence of 7 positive peaks, the brainstem auditory evoked potentials (BAEPs), which appear within the 5-7 ms from stimulus onset. BAEPs generally reflect activity in the auditory nerve and brainstem relay centres (Møller, 1999). The later BAEPs, however, may also reflect the activity of structures as high as the thalamus (Vaughan & Arezzo, 1988). The BAEP is much affected by manipulation of stimulus features such as its intensity or rate of presentation (Picton, Stapells, & Campbell, 1981) but is relatively unaffected by the manipulation of more psychological factors such as attention (Connolly, Aubry, McGillivary, & Scott, 1989). Indeed, the BAEP is robustly recorded even in unconscious states such as sleep (Campbell & Bartoli, 1986; Bastuji, Garcia Larrea, Bertrand, & Mauguière, 1988).

Middle-latency ERPs are observed in the 10-50 ms from stimulus onset. The middle-latency ERPs include N_o at about 10 ms, followed by P_o, a positive peak at 12 ms, N_a, a negative peak at 16 ms, P_a, a positive peak at 25 ms, and N_b, a negative peak at about 36 ms (Picton, Hillyard, Krausz, & Galambos, 1974). The origins of these potentials remain disputed, but it is generally accepted that the ERPs of the middle latency response receive contributions from the thalamocortical pathway (Kraus & McGee, 1995). At faster rates of presentation, sequential MLRs begin to overlap and sum to a steady-state response (SSR) that matches the periodicity and phase of the repeating stimulus (Regan, 1982).

Following the middle-latency components is a series of deflections that compose the so-called “vertex potential”, a complex wave consisting of a negativity around 100 ms and a positivity around 180 ms from stimulus onset (Butler, 1968). The “vertex potential” was so-named because it is largest when recorded by an electrode at the vertex (top) of the scalp, a location approximately analogous to the mid-central location (Cz) by modern standards. It is primarily composed of 2 ERP components labelled N1 and P2. The N1-P2 vertex potential is often preceded by P1, a positive component with a latency of approximately 50 ms (Picton, Hillyard, Krausz, & Galambos, 1974).

N1 was first discovered by Davis and colleagues, prior to the advent of averaging techniques (Davis, Davis, Loomis, Harvey, & Hobart, 1939). It is a negative, fronto-centrally maximal deflection peaking around 100 ms from stimulus onset, and inverts in polarity at the mastoid when a nose reference is used. The N1 occurs to all relatively abrupt changes in stimulus energy: stimulus onsets, as well as the offsets of long duration stimuli (Davis & Zerlin, 1966). In 1987, Näätänen and Picton performed a classic and much-cited review of the N1 literature to determine its component structure (Näätänen & Picton, 1987). They concluded that the N1 response was made up of three bilateral ERP components. The first is a supratemporal component that peaks at about 100 ms and is maximal over fronto-central areas of the scalp and inverts in polarity at the mastoid (Vaughan & Ritter, 1970). The second is a T complex, so-named because it is maximal over temporal regions of the scalp, peaking at about 140-150 ms. The T-complex originates in auditory association cortex on the lateral surface of the temporal lobe (Wolpaw & Penry, 1975). The third component is poorly understood and is labelled as a non-specific component whose generators are not entirely known (Hari, Kaila, Katila, Tuomisto, & Varpula, 1982). This component peaks at about 120 ms and is best observed when stimuli are presented very slowly (inter-stimulus interval $\geq$ 10 s). It is maximal at the vertex and might involve activity in the frontal lobes.

Using MEG, the N100m (magnetic counterpart of the supratemporal N1) has been sourced to a location near the posterior primary auditory cortex (Sams, Hämäläinen, Antervo, Kaukoranta, Reinikainen, & Hari, 1985). The N100m also appears to reflect the activity of neuronal populations that are tonotopically and ampliotopically organized (Pantev, Hoke, Lütkenhöner, Anogianakis, & Wittkowski, 1988; Pantev, Hoke, Lehnertz, & Lütkenhöner, 1989). Thus the N1 appears to reflect, as least in part, stimulus-specific activity in or near the primary auditory cortex.

P1 and P2 are not as well understood as N1. Early research quantified the vertex potential, and often N1, as a peak-to-peak measure from N1 to P2. This practice is only valid under the assumption that P2 represents essentially the same neural mechanisms as N1. Increasing evidence, however, suggests that this assumption is incorrect. Stimulus properties such as sound intensity and frequency do not equally affect N1 and P2 (Crowley & Colrain, 2004). The magnetic counterparts of P1 and P2 have been attributed to source generators located close to N100m on the supratemporal plane (Sams, Hämäläinen, Antervo, Kaukoranta, Reinikainen, & Hari, 1985). Nevertheless, their generators appear to be quite distinct. Furthermore, patients with unilateral temporal-parietal lesions demonstrate smaller N1 amplitudes, but P2 amplitude is preserved (Knight, Hillyard, Woods, & Neville, 1980). Thus, P2 may not depend on the neural processes indexed by N1.

All of the above-mentioned ERPs are typically classified as *exogenous* or *obligatory*. Again, this implies that they are mainly affected by physical and temporal features of stimulation, and not by the relevance of the stimulus to the organism (Näätänen, Simpson, & Loveless, 1982). Most other long latency ERP components are considered to be *endogenous*, and thus only partly relate to the physical parameters of the evoking stimulus. They will not be necessarily elicited by the stimulus but may optionally be elicited depending on psychological factors, such as if the subject is actively attending to the channel in which the stimulus is embedded or if the stimulus is relevant to the subject. Endogenous components, therefore, tend to vary with manipulations of the task demands assigned to the subject. Endogenous components often have a longer latency than exogenous ERPs, and are slow to develop, but in some cases may begin relatively early (Donchin, Ritter, & McCallum, 1978). Some endogenous components will be discussed later, with reference to the cognitive mechanisms that they signal.

2. Attention and Näätänen's Model

Incoming auditory stimuli therefore, are processed in an ascending series of structures that encode features like tonal frequency and intensity from as early as sensory transduction. Other features, such as location and temporal cues are computed higher in the brainstem. At the level of the auditory cortex, auditory events begin to acquire complex structure, and meaning. The neural activity associated with most stages of auditory information processing is reflected by ERP components.

All stimuli, however, are not processed equally. Those that are pertinent to current goals tend to enter conscious awareness preferentially, while those that are irrelevant fail to be processed entirely. Somehow, however, the observer must extract features from incoming stimulus input and determine whether these features match those that that have been deemed to be relevant. If they match, further processing should continue. If they fail to match, processing should cease. The operations involved in this "selective" attention process have been debated for more than 50 years. Broadbent (1958) recognized very early that humans have a limited ability to consciously process incoming information, and as such, they must select from the available inputs those that are relevant to current goals (Broadbent, 1958). Because only a limited amount of sensory input can be processed consciously, the central processing space that is associated with conscious perception is often referred to as the "limited capacity system". In structural models of attention, there is an information processing "bottleneck" at the point where information processing transitions from the relatively high-capacity pre-conscious system to the limited-capacity conscious system. A critical question in attention research, therefore, is the location of this bottleneck.

Risto Näätänen described his model of attention and auditory information processing in 1990. The great strength of Näätänen's model is that it uses evidence from ERP research. As described in the section 1.2, ERPs provide chronometric measures that track the course of information processing through the nervous system. Because it is built around ERPs, Näätänen's model was the first to demonstrate how neural processing differs between attended and unattended sensory channels. Like many other models of attention (e.g., (Broadbent, 1958; Deutsch & Deutsch, 1963; Norman, 1968; Treisman, 1964)), Näätänen's is a structural model with a bottleneck between pre-conscious and conscious processing.

In describing his model, Näätänen often refers to the concept of "automaticity". The automatic-conscious division was proposed by Posner and Snyder (1975a,b) when formulating their own (non-structural) model of attention. In structural models of attention, the automatic-conscious classification system is extremely useful for evaluating whether a stage of information processing operates before, or after the bottleneck that separates high capacity pre-conscious processing from limited capacity central processing. According to Posner and Snyder, an automatic process must fulfill 3 requirements: it should occur without intention, it should not give rise to conscious awareness, and it should not interfere with other ongoing mental activity. If a stage of information processing violates one of these requirements, it is considered to occur within the conscious mode of processing (Posner & Snyder, 1975; Posner & Snyder, 1975). Similar distinctions were made by Schneider and Shiffrin (1977) who used the term "controlled" rather than "conscious" processing (Schneider & Shiffrin, 1977).

More recently, the concept of weak automaticity has been introduced as a slight modification to Posner and Snyder's classification scheme. Weak automaticity lies between what they deemed automatic and conscious processing: a weakly automatic mechanism is capable of operating in the absence of attention, but can be influenced by it. By this new scheme, processing that operates entirely independently of attention is called strongly automatic (Hackley, 1993).

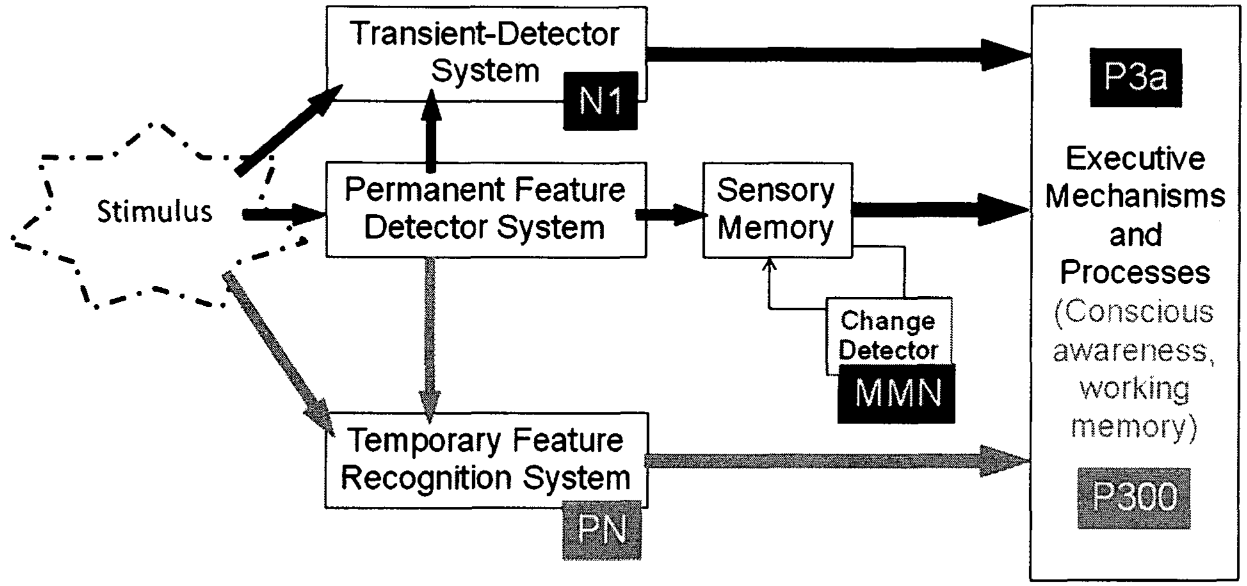

Figure 1: Näätänen's model of attention and auditory information processing.

Näätänen's model is illustrated above. This illustration has been modified from his classical representation for clarity. The model contains 3 routes to consciousness, represented by the 3 arrows that lead to the limited-capacity central executive. The term "task-independent" is used collectively to refer to the two passive information processing systems (illustrated by paths with black arrows). These mechanisms operate independently of current task demands, and take place prior to awareness that the stimulus was presented. This is termed pre-conscious (or pre-attentive) processing. Conscious awareness occurs via these passive routes as a result of interruption of the central executive and a subsequent switching of attention away from ongoing cognitive activity and toward the auditory channel. This is called “attention capture,” “passive” or “involuntary” attention because the observer was not actively engaged in attending to and becoming conscious of this specific stimulus input. The passive switching of attention from the task at hand may lead to a deterioration in performance (because fewer resources are available for task-relevant processing), and this phenomenon is known as “distraction”.

The “task-dependent” portion of Näätänen’s model (illustrated with gray arrows) is responsible for active, voluntary selective attention. Much of the historical foundation for Näätänen’s model lies in his treatment of information processing during active, selective attention, therefore the detailed discussion of Näätänen’s 3 routes to consciousness will begin with the “task-dependent” route.

2.1 The Temporary Feature Recognition System and the Processing Negativity

The “temporary feature recognition system” is the mechanism responsible for active, task-dependent processing in Näätänen’s model. This process is also known as selective attention. A critical question in the study of selective attention is how stimuli that are attended are processed differently than those that are not attended. Based on behavioural findings, some early researchers contended that unattended sensory input was filtered out (Broadbent, 1958; Hernández-Peón, Scherrer, & Jouvet, 1956), or attenuated (Treisman, 1964), at an early stage of processing. Psychophysiological research using ERPs provides a means to actually measure how neural processing differs between attended and ignored auditory stimuli. This research has yielded a fairly consistent pattern of results. There is no effect of attention on BAEPs (Woods & Hillyard, 1978; Picton & Hillyard, 1974; Davis & Beagley, 1985; Hillyard, Woldorff, Mangun, & Hansen, 1987; Connolly, Aubry, McGillivary, & Scott, 1989; Picton, Stapells, & Campbell, 1981). Some effects of attention appear to manifest at the level of the middle-latency response (McCallum, Curry, Cooper, Pocock, & Papakostopoulos, 1983; Hillyard, Woldorff, Mangun, & Hansen, 1987; Woldorff, Hansen, & Hillyard, 1987; Woldorff & Hillyard, 1991).

Before effects of attention were observed in the middle-latency potentials, however, the earliest attention-related modulation of an ERP component was observed in the N1 latency range. Hillyard and colleagues (1973), using a dichotic listening paradigm, demonstrated an enhancement of N1 called the "N1 effect", which they contended reflected an early selection mechanism that operated by preferentially processing stimuli entering via a selected channel of input (Hillyard, Hink, Schwent, & Picton, 1973). Numerous studies replicated the "N1 effect" of selective attention, providing proof for relatively early selection (Picton & Hillyard, 1974; Fujiwara, Nagamine, Imai, Tanaka, & Shibasaki, 1998; Hillyard, Woldorff, Mangun, & Hansen, 1987; Woldorff, Hansen, & Hillyard, 1987; Woldorff & Hillyard, 1991; Hackley, Woldorff, & Hillyard, 1987; Schwent & Hillyard, 1975).

Näätänen, however, contended that even an active selection process performed on the analyzed features of an incoming stimulus could be carried out rapidly enough to result in very early ERP effects (Näätänen, 1975). Using a slower rate of presentation, Näätänen and colleagues dissociated the negative enhancement observed with attention from the N1, and named this endogenous negative enhancement the processing negativity, or PN (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Gaillard, & Mäntysalo, 1980). Näätänen argued that the "N1 effect" simply reflected an earlier onset of the PN (Näätänen, Gaillard, & Mäntysalo, 1980). In short, because the intracerebral sources of the N1 and PN had similar voltage distributions on the scalp and occurred at the same time, they overlapped and summated spatially and temporally.

The PN is a theoretical concept that represents the attention-related processing that the attended and unattended channels receive. As such, it may be impossible to measure the full PN. Instead, a difference in PN is measured by the mathematical subtraction of the ERP that is elicited when the stimulus is unattended from that which is elicited when the stimulus is attended. This process removes common sensory processing, (note that the physical features of the stimulus are identical in the two instances; what varies is whether the stimulus is attended or not), and leaves the difference in the amount of PN that is allotted to the two stimuli. This is called the negative difference (Nd).

According to Näätänen, the PN reflects a comparison process in which the features of an incoming stimulus are compared to a memory trace defining task relevant stimuli. This memory is called the attentional trace. The attentional trace does not reflect all features of task relevant stimuli. Rather, only those features that differentiate "to-be-attended" from "to-be-ignored" stimuli are represented (Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989). The attentional trace takes some time to form. There is no Nd between attended and unattended stimuli for the first few stimuli of a sequence (Donald & Young, 1982). Most importantly, the attentional trace does not form automatically: it is a consequence of volition and effort, and it has a limited capacity (Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989). Higher intramodal task difficulty, resulting in higher attentional load, generates larger PN differences between the ERPs to stimuli in the attended and unattended channel than low load conditions (Alho, Woods, Algazi, & Näätänen, 1992). The formation of the attentional trace is thought to require a temporary connection between frontal lobe executive mechanisms and sensory memories located in the temporal lobes, causing a kind of "tuning" in secondary auditory cortices. Because Näätänen describes the PN as a reflection of a selection process that takes place on analyzed stimulus features, rather than a tonic preference for a channel of entry, his model stands in opposition to gain or filtering theories.

2.2 The Transient Detector System and N1

The first task-independent route to consciousness described in Näätänen's model is associated with the detection of abrupt changes in acoustic energy, such as stimulus onsets and offsets. According to Näätänen, such events are processed by the "transient detector system", whose output is reflected in the amplitude of the N1 ERP component. As described in section 1.2, the auditory N1 occurs to stimulus and offsets, with offset N1s occurring only to stimuli of relatively long duration. It is made up of 3 distinct ERP components: a supratemporal component, a T-complex, and a nonspecific component (Näätänen & Picton, 1987). The output of the transient detector system varies with the acoustic energy (or "intensity") of a stimulus.

It was apparent from very early in its discovery that the N1 has features that make it a very good candidate mechanism for passive (involuntary) attention. The N1 is large to the first stimulus in a sequence, and attenuates quickly upon subsequent repetition (Ritter, Vaughan, & Costa, 1968). This habituation means that, unlike the afferent activation patterns signalled by BAEPs and middle-latency ERPs, the N1 corresponds to the psychological phenomenon of "novelty" or "obtrusiveness". This habituation would protect the limited-capacity system from sensory overload. Different components of the N1 have different recovery times: the nonspecific component requires 1 minute, or longer, to fully recover (Näätänen & Picton, 1987), whereas the supratemporal component recovers in about 10 seconds (Mäkelä, Hari, & Leinonen, 1988). Näätänen considered the refractory period of the nonspecific component to be too long for it to subserve the conscious perception of auditory stimuli in general. Thus, the operation of the transient detector system is associated with the supratemporal N1.

The N1 appears to have some stimulus specificity, in the form of tonotopicity and ampliotopicity (Pantev, Hoke, Lütkenhöner, Anogianakis, & Wittkowski, 1988; Pantev, Hoke, Lehnertz, & Lütkenhöner, 1989). Nevertheless, the presentation of other tonal frequencies, and even the presentation of stimuli in other sensory modalities, can diminish the amplitude of the N1 (Butler, 1968). As such, the attention trigger represented by the N1 might signal, at least in part, a general change of state in the environment, rather than serving as a direct channel for sensory information (Davis & Zerlin, 1966). Indeed, the amplitude of the N1 is associated with stimulus detection, but not pitch recognition (Parasuraman, Richer, & Beatty, 1982). Näätänen (1975) described this phenomenon as "responding to something happening" (Näätänen, 1975). Given that the scalp-recorded N1 receives contributions from at least 3 independent ERP components, it is not surprising that the N1 can display both stimulus-specificity and generalization.

The threshold for attention switching in Näätänen's model is determined by the momentary excitability of the brain mechanisms responsive to the current stimulus, and the direction and intensity of attention at the moment of presentation. If the output of the transient detector system, as reflected by the amplitude of N1, is large enough to exceed this momentary threshold, an interrupt will be sent to the central executive and attention will be involuntarily drawn from ongoing tasks to the unattended channel. This attention switch is typically indexed by the P3a ERP (Squires, Squires, & Hillyard, 1975). Naatanen indicates that although the operations of the transient detector system are "task independent", the actual effectiveness of the interrupt can be affected by a number of factors including current demands being made on the central executive. If a stimulus is extremely obtrusive, it may also elicit the P3b, an ERP that is typically associated with active target detection. P3b is generally thought to signal the updating of memory representations (Donchin, 1981). P3a occurs slightly earlier (250-300 ms) than P3b (300-450 ms) and has a more centro-frontal scalp topography than the more parietal maximum P3b (Squires, Squires, & Hillyard, 1975).

2.3 The Change Detection System and the MMN

The present thesis studies the second task-independent route to conscious awareness described in Näätänen's model. This second task-independent route is much more complex than the transient detector system associated with N1. Rather than abrupt changes in energy, Näätänen's second task-independent system detects when an incoming stimulus violates some invariant feature of the preceding auditory sequence. This can be any feature of the stimulus such as location, frequency, duration, or even a decrease in intensity. By contrast, the output of the transient detector system only increases with an increase in stimulus intensity. As illustrated in Figure 1, the output of this second passive system is reflected by a different negativity, the Mismatch Negativity ("MMN"). Though there is no name explicitly given to the mechanism underlying the MMN ERP in Näätänen's (1990) model, it is often referred to as the "change detection system". The task-independent transient and change detection processing systems operate in parallel and may be based, at least in part, on different sensory mechanisms.

The MMN has its historical origins in the so-called "oddball paradigm". In the oddball paradigm, a sequence of physically identical standard stimuli is interrupted at rare and unpredictable times by a deviant stimulus with some changed feature. In 1975, Squires, Squires and Hillyard demonstrated that deviants in an oddball paradigm, whether attended or not, elicited an enhanced negativity (labelled as N2 to distinguish it from N1) around 200 ms from deviant stimulus onset (Squires, Squires, & Hillyard, 1975). Under dichotic listening conditions, Näätänen and colleagues also observed a similar negative enhancement to deviant stimuli. Since this N2 appeared to index the brain's ability to detect that a deviant stimulus did not match the memory trace for the standard, Näätänen and colleagues (1978) named the N2 the "mismatch negativity" (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Gaillard, & Mäntysalo, 1980).

Until 1982, the terms mismatch negativity and N2 were used interchangeably. Näätänen, Simpson, & Loveless (1982) suggested that N2 might be separable into two components, N2a (MMN) and N2b, with the N2a reflecting a neuronal mismatch process, and the N2b being an endogenous component that was elicited only when active attention was paid to the eliciting stimuli (Näätänen, Simpson, & Loveless, 1982). Later studies confirmed that the MMN was elicited by unattended, rare deviant stimuli, while the N2b was elicted by active detection of these deviants (or "targets") , or very obtrusive deviant stimuli that presumably caused distraction and attention switching towards the "to-be-ignored" channel (Sams, Alho, & Näätänen, 1984; Sams, Paavilainen, Alho, & Näätänen, 1985).

The MMN is a negative displacement in the ERP response to deviant stimuli, relative to the response to the standard, that peaks around 100-250 ms from stimulus onset. It is best observed in a difference wave, in which the ERP response to the standard is subtracted point-by-point from the response to the deviant. Both the standard and deviant stimuli elicit exogenous, sensory related ERPs, most notably the N1-P2 complex. Assuming that the deviant is only slightly different from the standard, the two stimuli should elicit similar sensory-related ERPs. The subtraction process removes the common potentials associated sensory-related processing, leaving only the potentials associated with the detection of change. The MMN is maximal at fronto-central sites, is typically largest over the right hemisphere, and inverts at sites below the Sylvian fissure when the nose is used as reference. This scalp distribution has been attributed to three generators: two vertically-oriented dipoles on the supratemporal plane and one right frontal generator. The supratemporal generators of the MMN are thought to reflect the actual change detection mechanism, while the frontal generator is thought to reflect a call for attention switching (Giard, Perrin, Pernier, & Bouchet, 1990). Like the N1, when the MMN is large enough to exceed the momentary threshold for attention switching, the involuntary attention switch that follows is signalled by the P3a (Escera, Alho, Schröger, & Winkler, 2000).

The MMN can be elicited by deviants in an oddball paradigm that differ from the standard along any physical dimension, including tonal frequency (Näätänen, Gaillard, & Mäntysalo, 1978), intensity (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989), and spatial location (Schröger & Wolff, 1996). Changed temporal features, such as duration (Näätänen, Paavilainen, & Reinikainen, 1989) or inter-stimulus interval (Nordby, Roth, & Pfefferbaum, 1988) can also elicit an MMN. Furthermore, the MMN can be elicited under a wide range of conditions beyond the classic oddball paradigm.

Picton and colleagues (2000) outlined 5 types of invariance (also called regularities) that, when violated, can elicit an MMN: *simple* invariance, *complex* invariance, *hypercomplex* invariance, *pattern* invariance, and *abstract* invariance. Simple invariance occurs in the classic oddball paradigm: all standard stimuli are identical, and the deviant can differ from the standard along any dimension, such as tonal frequency, intensity, location, or duration. In complex invariance, the standard stimuli are not identical, but they have some feature in common. For instance, a sequence of standard stimuli may vary randomly in frequency and intensity, but share the same duration. In this instance, an MMN can be elicited to duration-change deviants (Gomes, Ritter, & Vaughan, 1995).

Hypercomplex invariance is established when standards are physically different, but their features are governed by rules that dictate their feature combinations. For instance, if 3 standard stimuli are defined by specific combinations of tonal frequency and intensity, and an incoming stimulus has the frequency of standard 1, but the intensity of standard 3, an MMN will be elicited (Gomes, Bernstein, Ritter, Vaughan, & Miller, 1997). In pattern invariance, temporal rather than physical features of the standard stimuli are violated. For instance, if an alternating pattern of two tones is violated by a stimulus repetition, an MMN will be generated (Nordby, Roth, & Pfefferbaum, 1988). Constant ISI also constitutes a type of pattern invariance. Finally, abstract invariance may consist of a pattern in which the physical features of the constituent tones are varied, such that only the relationships between those tones remain invariant. For example, in a standard tone pair, the second tone may be 300 Hz higher than the first tone. While the actual tonal frequencies of the tones may vary randomly, this relationship between the first and second tone is maintained. Deviant pairs violate this invariant relationship, perhaps by repeating the same stimulus in the second position of the pair, or by containing a second tone that is lower, rather than higher, in frequency than the first tone (Saarinen, Paavilainen, Schröger, Tervaniemi, & Näätänen, 1992). Abstract invariance may also involve a continued relationship between successive tones. One example of such a paradigm is one in which the standard tones continuously descend a musical scale, and deviants are infrequent increases or repetitions of tonal frequency (Tervaniemi, Maury, & Näätänen, 1994).

Regardless of the type of invariance that is violated to elicit the MMN, the critical requirement for MMN elicitation is that a memory is formed to represent what is "standard" or "invariant" in the auditory sequence. The MMN is not elicited by the first stimulus in a sequence: two or three presentations of the standard must be made before a deviant elicits an MMN (Sams, Hämäläinen, Antervo, Kaukoranta, Reinikainen, & Hari, 1985). This suggests that a neuronal model (a memory for the past stimulus events) must be built up before the MMN can be elicited.

Näätänen (1990) conceived the change detection mechanism underlying MMN generation as a memory comparison process in which incoming stimuli are compared to a neuronal trace of previous standard stimuli. Specifically, the change detection mechanism underlying MMN generation is thought to operate on a relatively long-lasting form of auditory sensory memory. This stage of auditory sensory memory has been referred to by different researchers as the long auditory store (Cowan, 1984), echoic memory (Neisser, 1967), or the stimulus representation (Näätänen & Winkler, 1999). Näätänen and Winkler (1999) describe the stimulus representation as the stage of memory in which the physical features of incoming stimuli, which have been extracted separately and temporarily stored in separate buffers, become integrated into a unitary memory representation based upon their temporal proximity.

Estimations of the duration of this memory trace vary depending on the paradigm used. Manipulations of the interstimulus interval (ISI) reveal that the memory trace may last as little as 2-3 seconds (Mäntysalo & Näätänen, 1987). However, studies manipulating the duration of a silent interval between trains of stimuli (the inter-train interval) have demonstrated that the memory underlying the MMN can be reactivated after only one standard stimulus presentation following inter-train intervals as long as 30 s (Winkler et al., 2002). The reason for this disparity is thought to be that studies manipulating ISI actually place the deviant stimulus out of context (i.e., there is no contextually relevant standard for the deviant to be compared to) before reaching the temporal limits of the sensory memory trace (Cowan, Winkler, Teder, & Näätänen, 1993).

The amplitude of the MMN appears to correspond to the strength of the underlying memory trace. When the ISI between standard stimuli is short, the MMN tends to be larger

(Näätänen & Picton, 1987; Sabri & Campbell, 2001; Javitt, Grochowski, Shelley, & Ritter, 1998; Alain, Woods, & Ogawa, 1994). Furthermore, when the representation of the standard is strongly reinforced, by increasing the number of standard stimuli presented between successive deviants, MMN amplitude increases (Imada, Hari, Loveless, McEvoy, & Sams, 1993). This effect is thought to underlie the relationship between MMN amplitude and the probability of the deviant stimulus. As deviant probability decreases, the size of the MMN increases (Näätänen, Sams, Järvilehto, & Soininen, 1982; Sinkkonen, Kaski, Huotilainen, Ilmoniemi, Näätänen, & Kaila, 1996; Javitt, Grochowski, Shelley, & Ritter, 1998; Shelley, Silipo, & Javitt, 1999; Sato, et al., 2000; Sabri & Campbell, 2001; Sonnadara, Alain, & Trainor, 2006; Sato, et al., 2003).

Deviant probability and ISI also interact in an important way: if two sequences have the same deviant probability, but different ISIs, the amount of time between successive deviant stimulus presentations will be different. For this reason, some researchers refer to the proportion of deviants in a sequence as the sequential probability. The amount of time between deviant presentations is referred to as the temporal probability. Both sequential and temporal probability affect the amplitude of the MMN (Sabri & Campbell, 2001). The effect of temporal probability is thought to result from the formation of a memory for the deviant stimulus itself (Sams, Alho, & Näätänen, 1984). If a representation of the deviant stimulus exists in sensory memory, the memory comparison mechanism will find deviants to be a memory "match" rather than "mismatch", and no MMN may be elicited.

The MMN is also strongly tied to the perceptibility of the deviant. In a passive frequency oddball paradigm, an MMN is only elicited by frequency differences that can be detected under corresponding active task conditions (Näätänen & Alho, 1995). The amplitude of the MMN increases, and its latency decreases with increasing frequency separation between standard and deviant tones (Tiitinen, May, Reinikainen, & Näätänen, 1994). Similarly, the amplitude of the MMN to repetition deviants increases with the frequency separation between the two tones presented in an alternating pattern (Alain, Woods, & Ogawa, 1994). Because of its relationship with ISI, deviant probability, and the contents of perception, the MMN is considered to be very strongly tied to the strength and accuracy of auditory sensory memory (Näätänen & Alho, 1997).

2.4 Näätänen's Model in Review

Näätänen's (1990) model of attention and auditory information processing, therefore, defines 3 routes by which information can enter the central, limited capacity system associated with conscious perception. One of these routes, associated with the "temporary feature detection system", is responsible for active, voluntary attention, and is associated with the PN. Two passive, task-independent routes are also described, involving the "transient detection system" reflected by N1, and the "change detection system" reflected by the MMN. According to Näätänen's model, the differential processing of attended and unattended stimuli occurs relatively late in information processing. The PN, reflecting active selection of the "to-be-attended" input, is thought to reflect processes carried out on analyzed stimulus features at the level of the secondary auditory cortex. Näätänen places even more importance, however, on the MMN in evaluating the degree to which auditory stimuli are processed in the absence of attention.

> "How far do strongly automatic ... fully attention-independent processes extend in auditory processing? There [is] one ERP component, namely the MMN, which [can] be used in assessing automaticity in auditory sensory processing in terms of the actual information extraction and flow. The occurrence of the MMN to slightly deviant stimuli in the absence of attention suggests that the sensory stimulus features are fully processed

> independently of attention. This is because a sensitive response to a deviation in an unattended input would have been impossible unless the neuronal traces underlying MMN generation had not contained fully processed sensory information." (p.229)

Consequently, the automaticity of the MMN has been extensively studied. The automaticity of the MMN, however, is also a tremendously important issue for clinical and applied research. Alterations of cognitive function are thought to form the basis of many developmental, neurological, and psychiatric disorders. Unfortunately, almost all measures of cognitive function require the patient to maintain attention. In the classic Näätänen model, the MMN is claimed to be elicited indepedently of attention (i.e., automatically). As such, the MMN has proven to be extremely useful in the clinical and applied fields (Näätänen, Paavilainen, Rinne, & Alho, 2007). If, however, the MMN is not an automatic mechanism, then such clinical and applied research must carefully control for possible attention effects. The extensive usefulness of the MMN in both basic and clinical research requires that the assumption of the automaticity of the MMN be thoroughly tested.

3. *Automaticity and the MMN*

3.1 Attention and the Automaticity of the MMN

The automaticity of the MMN is often tested by manipulations of attention. For the purpose of the current discussion, two categories of attention paradigms will be defined. "Direction of attention" studies are those in which attention is directed towards or away from a channel bearing MMN-eliciting deviants in separate conditions. Direction of attention studies have been carried out both within the auditory modality (usually dichotic listening), and under intermodal conditions with a passive diversion task presented in another modality (usually the visual modality). "Strength of attention" studies examine the effect of increasing attentional demands in a diversion task without ever having subjects direct their attention towards the auditory channel containing the MMN-eliciting stimulus sequence. The difficulty of the diversion task is often manipulated with the rationale being that a difficult task requires more (or "stronger") focussing of attention than an easy task, and as such, fewer attentional resources would be available for the processing of the irrelevant auditory channel containing the deviant.

In intermodal direction of attention studies, the MMN is compared when the auditory channel is actively attended (and the deviant is designated as a to-be-detected "target") and when it is ignored, by directing attention to a different modality, usually visual. In the ignore condition, the auditory deviant can only be detected, and the MMN thus elicited, through passive means. While the MMN often appears not to be enhanced by attention (Näätänen, Simpson, & Loveless, 1982; Sams, Alho, & Näätänen, 1984; Kathmann, Frodl-Bauch, & Hegerl, 1999), many studies have found the MMN to be larger under active than passive conditions (Woods, Alho, & Algazi, 1992; Alho, Woods, Algazi, & Näätänen, 1992; Alho, Woods, & Algazi, 1994; Müller, Achenbach, Oades, Bender, & Schall, 2002). Recall, however, that active detection of the deviant stimulus is also associated with the N2b. Thus, a major problem when comparing the MMN under active and passive conditions is that in the active condition, the MMN and the N2b are both elicited and may overlap both temporally and spatially. The larger negativity that is apparent in attend conditions, therefore, may reflect a difference in N2b amplitude rather than the MMN. The N2b can be dissociated from the MMN by its longer latency (Sams, Alho, & Näätänen, 1984; Sams, Paavilainen, Alho, & Näätänen, 1985), and its scalp distribution, which is more posterior than the MMN, and lacks polarity reversal at recording sites below the Sylvian fissure when the nose is used as a reference (Novak, Ritter, Vaughan, & Wiznitzer, 1990), but these differences can be subtle.

In intramodal direction of attention studies, the diversion task in passive conditions is also delivered in the auditory modality. This usually involves dichotic listening, in which two auditory oddball sequences are delivered, one to each ear. The deviants in the to-be-attended ear are designated as targets that the subject is asked to detect, while stimuli in the other ear are to-be-ignored. Woldorff and colleagues (1991) emphasized that paradigms for studying selective attention require certain parameters: stimuli should be presented at a very fast rate, channels of entry should be very easily distinguished, and the active task should be demanding. Thus, in their dichotic listening paradigm, the two channels are very physically different, and are defined not only by ear of entry, but also by tonal frequency. Tones are also delivered quite rapidly, and the active task requires subjects to respond to difficult-to-detect targets (small intensity decrement deviants). The MMN elicited to deviants when they were presented in the ignored ear was significantly smaller than when the same deviants were presented in the same ear but when it was attended (Woldorff, Hackley, & Hillyard, 1991). Thus, contrary to the Näätänen claim, attention did appear to affect the MMN.

Like intermodal direction of attention paradigms, an inherent problem of dichotic listening is that deviants occurring in the attended channel can elicit an N2b component (Näätänen, Simpson, & Loveless, 1982). Many dichotic listening studies recording from the mastoid to separate N2b from MMN have found that apparent MMN enhancement with attention was indeed attributable to N2b overlap (Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993; Paavilainen, Tiitinen, Alho, & Näätänen, 1993; Alho, Woods, & Algazi, 1994). This phenomenon likely also explains the observed effect of attention on MMN amplitude in some other dichotic listening studies that did not record from the mastoid (Alho & Sinervo, 1997; Szymanski, Yund, & Woods, 1999)

In order to avoid the N2b problem, Woldorff and colleagues (1998) conducted a high load dichotic listening study similar to that from 1991 using MEG. The N2b is not well registered by MEG recordings over temporal areas. Thus any attention-related changes in the magnetic equivalent of the MMN (the mismatch field, MMF) must correspond to modulation of the MMN, and not N2b overlap. The MMF to deviants in the attended ear was significantly larger than that to deviants in the unattended ear. Indeed, the MMF to deviants in the unattended ear failed to reach statistical significance (Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998). N2b overlap also fails to provide a sufficient explanation for two studies performed by Alain and colleagues. Arnott and Alain (2002) found significant modulation of the MMN at both frontal and mastoid sites when subjects selectively listened to 1 of 3 virtual locations (Arnott & Alain, 2002). Alain and Woods (1997) also demonstrated modulation of the MMN with attention, this time in a dichotic listening task, and using an auditory pattern, rather than oddball stimuli. This effect was confirmed at the mastoid, but only under conditions where pattern violations in the attended ear was designated as a targets (Alain & Woods, 1997).

There exists, however, an interpretation for these apparent attention effects that does not challenge the automaticity of the MMN. In 2003, Sussman and colleagues suggested that the comparison mechanism underlying MMN generation operates with a feature-specific limited capacity. This means that, in dichotic listening, if the targets in the attended ear and the deviants in the unattended ear are both intensity deviants, these two deviants compete for access to the limited resources of the comparator mechanism. This effect is especially strong if the attended target and the unattended deviant have identical values along the dimension of deviance, for instance, if they are both intensity decrement deviants with an intensity of 75 dB. Under conditions of feature-specific competition, the comparison mechanism underlying MMN generation facilitates task performance by becoming biased towards detecting deviants (targets) in the attended ear. If, on the other hand, the deviants in the two ears vary along different physical dimensions (for instance, if the target in the attended ear is an intensity deviant, while frequency deviants are presented in the unattended ear), there is no competition for resources in the comparison mechanism, and the MMN to deviants in the unattended ear should not be diminished (Sussman, Winkler, & Wang, 2003).

Shalgi and Deouell (2007) demonstrated that feature-specific competition influences the temporal, but not the frontal, component of the MMN (Shalgi & Deouell, 2007). Thus, the effects of feature-specific competition would manifest as MMN amplitude changes even at mastoid sites. Feature-specific competition, therefore, provides a viable explanation for MMN modulation in those intramodal direction of attention studies that have avoided N2b overlap (Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998; Alain & Woods, 1997; Arnott & Alain, 2002). As such, these intramodal studies do not challenge the automaticity of the MMN: they merely demonstrate that the comparison mechanism underlying the MMN operates with a limited processing capacity.

Strength of attention studies are those in which the MMN is only examined under passive conditions. In this case, attentional demands are manipulated by varying the demands of the diversion task. Strength of attention studies, therefore, avoid the confounding influence of N2b overlap by never directing attention towards the MMN-eliciting auditory sequence. The majority of strength of attention studies employ a visual diversion task. Most of these have found no modulation of the MMN with the difficulty of the diversion task (Alho, Woods, Algazi, & Näätänen, 1992; Dittmann-Balcar, Thienel, & Schall, 1999; Harmony, et al., 2000; Otten, Alain, & Picton, 2000; Dyson, Alain, & He, 2005; Muller-Gass, Stelmack, & Campbell, 2005; Muller-

Gass, Macdonald, Schröger, Sculthorpe, & Campbell, 2007; Muller-Gass, Stelmack, & Campbell, 2006). However, many of these studies employed visual tasks with discrete stimuli, which may have allowed subjects to switch attention between modalities in the break between visual stimulus presentations. Those few intermodal strength of attention studies that have demonstrated modulation of the MMN with the demands of the diversion task all employed visual tasks with continuous stimuli (Kramer, Trejo, & Humphrey, 1995; Yucel, Petty, McCarthy, & Belger, 2005; Restuccia, Della Marca, Marra, Rubino, & Valeriani, 2005; Zhang, Chen, Yuan, Zhang, & He, 2006).

In summary, some few studies have yielded an effect of attention on the MMN. Intramodal direction of attention studies reducing (Alain & Woods, 1997; Arnott & Alain, 2002), or eliminating the contribution of N2b (Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998), have demonstrated amplitude differences between the MMNs elicited by attended-ear targets and unattended-ear deviants. These effects, however, can be explained by feature-specific competition (Sussman, Winkler, & Wang, 2003). Most studies that have demonstrated susceptibility of the MMN to attentional demands, while avoiding N2b overlap and feature-specific competition, have been intermodal strength of attention studies employing continuous visual diversion tasks (Kramer, Trejo, & Humphrey, 1995; Yucel, Petty, McCarthy, & Belger, 2005; Restuccia, Della Marca, Marra, Rubino, & Valeriani, 2005; Zhang, Chen, Yuan, Zhang, & He, 2006). The results of these studies are inconsistent, but do suggest that the MMN is not strongly automatic.

3.2 Sleep and the Automaticity of the MMN

Any operation that is considered to be automatic should be carried out at the pre-conscious level (i.e., prior to the subject being conscious that the stimulus has been presented).

Thus, some of the most convincing evidence for the automaticity of the MMN has been obtained in unconscious states, in which it is extremely unlikely that subjects are attending to (and conscious of) the auditory stimuli. The MMN can occasionally be observed in coma, typically when subjects are emerging from it (Fischer, Luauté, Adeleine, & Morlet, 2004; Fischer, Morlet, & Giard, 2000; Fischer, Morlet, Bouchet, Luaute, Jourdan, & Salord, 1999), as well as in vegetative states (Wijnen, van Boxtel, Eilander, & de Gelder, 2007), and under anaesthesia (Koelsch, Heinke, Sammler, & Olthoff, 2006). Findings in these abnormal states, however, may not apply to the healthy brain. Therefore, the majority of studies which test whether the MMN operates at the pre-conscious level do so using natural sleep.

Auditory processing during sleep is not the same as in the waking state (Velluti, 2008). BAEPs are unaffected by sleep (Amadeo & Shagass, 1973; Osterhammel, Shallop, & Terkildsen, 1985; Campbell & Bartoli, 1986; Deacon-Elliott, Bell, & Campbell, 1987). The earliest ERPs to be affected by sleep are the middle-latency components, which are attenuated (Osterhammel, Shallop, & Terkildsen, 1985; Linden, Campbell, Hamel, & Picton, 1985; Jerger, Chmiel, Frost, & Coker, 1986). Most notably, the decline in auditory sensitivity during sleep onset is accompanied by a decline in the amplitude of the N1 (de Lugt, Loewy, & Campbell, 1996; Ogilvie, Simons, Kuderian, MacDonald, & Rustenburg, 1991).

Once definitive sleep is reached, the pattern of long-latency auditory ERPs that is observed varies by stage. Natural sleep is composed of a series of stages, including non-REM (NREM) stages 1–4, reflecting the depth of sleep, and REM sleep. In NREM, the output of transient detector system appears to be inhibited. N1 is reduced to near-baseline level regardless of the intensity of the stimulus or its rate of presentation. On the other hand, P2 often appears to be larger in amplitude compared to the waking state (Crowley & Colrain, 2004). Campbell and

Colrain (2002) explain the reduction of the N1 and enhancement of the P2 to be a result of the removal of the waking negative-going attention-related PN (wPN) (Campbell & Colrain, 2002). In order to allow sleep to occur, consciousness of the external environment and thus attention-related processing, as reflected by the PN, must be inhibited. Recall that PN is also elicited by ignored stimuli, but less so compared to when they are attended. Thus, all attention-related processing must cease. Because the PN overlaps and summates with both N1 and P2, its removal results in N1 becoming much attenuated (it is less negative-going) but P2 actually becomes larger (it is also less negative-going, or more positive-going). During sleep, other very large amplitude ERPs such as a negative wave peaking at 350 ms (N350) appear if the stimulus is obtrusive. If the stimulus is very obtrusive and presented infrequently, a K-complex consisting of the large N350 (25-50 μV) and a late, extremely large N550 (100-200 μV) can be elicited (Loomis, Harvey, & Hobart, 1938; Bastien & Campbell, 1992; Salisbury & Squires, 1993; Cote, de Lugt, Langley, & Campbell, 1999; Cote, 2002). In REM sleep, N1 returns to 25-50% of its amplitude in the waking state (Colrain & Campbell, 2007).

Most studies have failed to demonstrate an MMN in stage 2 of NREM sleep (Loewy, Campbell, & Bastien, 1996; Nashida, Yabe, Sato, Sutoh, Shinozaki, & Kaneko, 2000; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Nittono, Momose, & Hori, 2001; Paavilainen, Cammann, Alho, Reinikainen, Sams, & Näätänen, 1987; Sallinen, Kaartinen, & Lyytinen, 1997; Winter, Kok, Kenemans, & Elton, 1995). Ruby and colleagues (2008) have demonstrated an MMN in stages 2 and 3, but the MMN has not been demonstrated in stage 4 (Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008). The general paucity of evidence for continued operation of the MMN in slow wave sleep (stages 3 and 4) may be due to the unique challenges of signal averaging in these stages. The amplitude of the background EEG in slow-wave sleep is very high (often > 200 μV), which can make the MMN (often < 1 μV) very difficult to observe (Sabri & Campbell, 2002).

Unlike NREM, the MMN is very consistently reported in REM sleep, often with an attenuated amplitude compared to the waking state (Atienza & Cantero, 2001; Atienza, Cantero, & Gómez, 1997; Atienza, Cantero, & Gómez, 2000; Loewy, Campbell, & Bastien, 1996; Nashida, Yabe, Sato, Sutoh, Shinozaki, & Kaneko, 2000; Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008; Sabri & Campbell, 2005). This evidence strongly suggests that the MMN operates at the pre-conscious level, and as such, is at the very least, weakly automatic.

4. The Problem of the Oddball Paradigm

There exists, however, a fundamental flaw with most of the research that has tested the automaticity of the MMN. Most of this research employed oddball paradigms, typically with frequency deviants. The frequency oddball paradigm is, indeed, the classic paradigm for evoking the MMN. Näätänen interpreted the MMN as the outcome of a "mismatch" between an incoming deviant stimulus and the memory representation of the standard. An alternative interpretation, however, is one of "fresh afferent" activation. Recall that the auditory system is tonotopically, and possibly also ampliotopically organized, from the cochlea through to the primary auditory cortex. This means that in a classic oddball paradigm, a deviant stimulus created by changing tonal frequency activates a different population of frequency-specific afferent neurons than does the standard. This is referred to as the "fresh afferents" theory of the MMN. Much evidence supports the idea that there is a "true" MMN response that is the consequence of a memory-based mechanism, and not fresh afferent activation (Näätänen, Paavilainen, Rinne, & Alho, 2007). In oddball paradigms, however, this true MMN is rarely elicited alone.

In oddball paradigms with tonal frequency deviants, the standard tone is presented repeatedly, and as such, the neurons of the afferent population responding to the tonal frequency of the standard will tend to be in a refractory state. Conversely, the neurons of the afferent population responding to the deviant will tend to remain fresh, and produce a large response when stimulated. The output of the transient detector system, reflected by N1, varies with the refractoriness of afferent neuronal populations (Näätänen & Picton, 1987). As such, N1 is larger to the infrequently presented deviant than to the frequently presented standard. The classic deviant minus standard difference wave computed under these circumstances includes both the MMN and an enhancement of N1.

Since N1 and the MMN occur in a similar latency range, and have similar scalp distributions, disentangling their contributions to the observed deviance-related negativity (DRN) requires the implementation of carefully-designed control procedures. Schröger and colleagues developed a technique to control for refractoriness effects in oddball paradigms as part of an effort to determine whether a memory-based comparison process indeed occurred in oddball paradigms. Schröger's technique involves a "control" sequence in which the deviant tone is presented at the same probability as it is in the oddball sequence, but amongst a number of other tones that vary along the dimension of deviance. For instance, a frequency deviant of 1200 Hz, presented at a probability of 0.10 in the oddball sequence, would be presented equiprobably among 9 other tones with different frequencies in the control sequence. The ERP to each tone in this control sequence should consist solely of the afferent activation pattern attributable to neuronal refractoriness. A "control" difference wave is then computed by subtracting the ERP to the control tone that matches the deviant from the ERP to the oddball deviant. This procedure should remove activity that is related to differential refractoriness, and leave intact only the "true" MMN.

Using this procedure, Schröger and colleagues examined the contribution of fresh afferent activation to a number of oddball paradigms. Location deviants elicit a DRN composed of MMN and N1 enhancement (Schröger & Wolff, 1996). Frequency deviants also do not elicit a "true" MMN, although the effect of N1 overlap can be minimized by using a small extent of deviance (Jacobsen & Schröger, 2001). Intensity increment deviants in an oddball paradigm cause N1 enhancement, but intensity decrements do not (Jacobsen, Horenkamp, & Schröger, 2003). N1 enhancement *per se* does not occur to duration deviants, but depending on the timing of the duration difference, the MMN may become overestimated or underestimated in the difference wave due to overlap with offset N1 responses (Jacobsen & Schröger, 2003). Furthermore, if the deviants in a duration oddball paradigm are created by reducing stimulus duration to below 200 ms, differences in perceived intensity also occur (Scharf & Houtsma, 1986). In summary, there are very few oddball paradigms that do not risk N1 enhancement.

Jacobsen and Schröger (2001) note that the risks associated with oddball paradigms are not limited to N1 enhancement in the difference waveform. Oddball paradigms also invite a computational risk. Not all neural activity is registered by electrical deflections at the scalp. Thus, even in the absence of N1 enhancement, differential afferent activation could be occurring, and if so, deviant tones may be detected without requiring a memory comparison process.

5. *The Present Thesis*

The goal of the present thesis is to examine the automaticity of the MMN using a paradigm that avoids fresh afferent activation. One way to avoid the fresh afferent activation that is inherent to oddball paradigms is to elicit the MMN by violating a more complex type of invariance. Recall that Picton and colleagues (2001) defined five different types of invariance that, when violated, elicit an MMN. Violations of some types of invariance other than the oddball, can also involve introducing a deviant with new simple features, thus risking fresh afferent activation. However, increasing the complexity of the paradigm too much also risks the possibility that some individuals will not be capable of automatically extracting the regularities of the sequence (Tervaniemi, Rytkönen, Schröger, Ilmoniemi, & Näätänen, 2001; Atienza, Cantero, & Dominguez-Marin, 2002). As such, the current thesis sought to use a relatively simple paradigm that nonetheless avoids the pitfalls of fresh afferent activation that are inherent to the oddball paradigm.

Pattern invariance can be quite simple, and yet avoid fresh afferent activation. The current thesis uses a two-tone alternating pattern similar to that developed by Nordby and colleagues in 1988. In this type of pattern, two tones of different tonal frequency, A and B, consistently alternate in the standard sequence (e.g., ABABABAB...). Deviants that violate this pattern are repetitions of either A or B (e.g., ABABAB**B**AB...). Because deviants in this paradigm are physically identical to the preceding standard, no fresh afferent activation should occur. Indeed, if anything, N1 should be reduced in response to such repetitions (Butler, 1968).

More specifically, the type of pattern employed in the current thesis is commonly known as an isochronous pattern. “Isochronous” means that there is no temporal grouping – the A and B tones of the pattern are always separated by the same ISI. Studies examining the rules of pre-conscious auditory object formation have demonstrated that increasing the time interval between tone pairs assists in the formation of tone pair “objects”. These tone pair objects appear to be relatively encapsulated in memory (Takegata, Roggia, & Winkler, 2005; Müller & Schröger, 2007). Alternating two-tone patterns are also defined in memory by simultaneously active representations for a hierarchy of structural rules (Horváth, Czigler, Sussman, & Winkler, 2001). These include "local" rules that describe the relationships between adjacent tones (e.g., B follows A, A follows B), and "global" rules that describe the overall composition of the pattern (e.g., every second tone is B). Like temporally-grouped patterns, an isochronous pattern can be defined by local and global rules, but unlike temporally-grouped patterns, an isochronous pattern does not appear to be represented in memory as a series of encapsulated auditory objects.

Apart from avoiding fresh afferent activation, another advantage of a two-tone alternating pattern is that it allows for manipulation of the amplitude of the MMN. In 1994, Alain and colleagues investigated the effects of tonal separation and rate of presentation on the MMN to violations of a two-tone alternating pattern. They found that having a smaller tonal separation between the two constituent tones of the pattern, or decreasing the rate of presentation decreased the amplitude of the MMN (Alain, Woods, & Ogawa, 1994). Several previous studies of the MMN and attention suggested that the MMN to small, but not large, deviants is susceptible to the effects of attention (Muller-Gass, Stelmack, & Campbell, 2006; Szymanski, Yund, & Woods, 1999; Woods, Alho, & Algazi, 1992; Alho, Woods, Algazi, & Näätänen, 1992). Presumably, this occurs because small deviants require a stronger and more precise sensory memory representation of the standard in order to be detected, and attention towards auditory stimuli enhances the sensory representation (Alain & Woods, 1997; Muller-Gass, Stelmack, & Campbell, 2006; Szymanski, Yund, & Woods, 1999). Thus, in the present thesis, the frequency separation between the two tones of the pattern is often manipulated.

Three main studies are carried out in the present thesis, each using a different, but complementary approach to study the automaticity of the MMN elicited by pattern violations.

5.1 Study 1

Study 1 examines the automaticity of the MMN by manipulating attentional demands. As reviewed in section 3.1, very few studies have demonstrated an effect of attention on the MMN that cannot be attributed to either N2b or feature-specific competition. Most of these have been intermodal strength of attention studies, in which the difficulty of a continuous visual task was varied (Kramer, Trejo, & Humphrey, 1995; Yucel, Petty, McCarthy, & Belger, 2005; Restuccia, Della Marca, Marra, Rubino, & Valeriani, 2005; Zhang, Chen, Yuan, Zhang, & He, 2006). All of these studies employed oddball sequences with moderate to large frequency deviants, and as such, may have received significant contributions from overlapping N1 enhancement. Study 1, therefore, is an intermodal strength of attention study, presenting subjects with "to-be-ignored" auditory patterns while they perform a demanding continuous visuospatial object tracking task at two levels of difficulty. To examine the possibility that small, but not large, MMNs are susceptible to the effects of attention, the two-tone alternating pattern is presented in two conditions: one in which the two tones of the pattern are separated by 1 semitone (A = 1000 Hz, B = 1059 Hz), and another in which the two tones are separated by 6 semitones (A = 841 Hz, B = 1189 Hz).

5.2 Study 2

Study 2 examines the automaticity of the MMN by presenting auditory patterns during natural sleep. As reviewed in section 3.2, the MMN is often observed in REM sleep. However, most of the studies that have demonstrated the MMN in sleep employed oddball paradigms with frequency deviants. To date, three sleep MMN studies have been performed using paradigms that should have avoided N1 enhancement (Loewy, Campbell, de Lugt, Elton, & Kok, 2000; Macdonald, Jamshidi, & Campbell, 2008; Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008). Of these, only one has succeeded in demonstrating an MMN during sleep (Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008). Ruby and colleagues employed an oddball paradigm with duration decrement deviants, which in principle should not have caused N1 enhancement (Jacobsen & Schröger, 2003). However, changing the duration of an auditory stimulus with a duration of less than 200 ms causes changes to its perceived intensity (Scharf & Houtsma, 1986). As such, the duration deviants employed by Ruby and colleagues may have caused fresh afferent activation. Thus, in Study 2, the two-tone alternating pattern was presented during one night of natural sleep. Again, since small MMNs may be more susceptible to modulation by attention than large MMNs, the auditory pattern was presented under conditions of 1 and 6 semitone separation.

5.3 Study 3

Study 3 takes a somewhat indirect approach to the automaticity of the MMN by studying a proposed mechanism for its susceptibility to attention. Several studies that have demonstrated an apparent modulation of the MMN by attention claimed that the MMN is larger to attended stimuli because attention enhances the strength and precision of the memory trace for the standard (Muller-Gass, Stelmack, & Campbell, 2006; Szymanski, Yund, & Woods, 1999; Alain & Woods, 1997). Study 3, therefore, examined whether the amplitude of the MMN does indeed vary with the strength of the memory for the standard. As reviewed in section 2.3, there are two principal techniques for manipulating the strength of the memory for the standard: changing the ISI (Sams, Hari, Rif, & Knuutila, 1993), and changing the number of standards presented between deviants (Imada, Hari, Loveless, McEvoy, & Sams, 1993).

Increasing ISI is impractical in a patterned stimulus paradigm because slow rates of presentation risk loss of the perception of a pattern (Sussman, Ritter, & Vaughan, 1998). Study 3 therefore manipulates the probability of deviant occurrence. To date, all of the studies that have demonstrated an effect of deviant probability on the MMN have employed oddball paradigms with frequency deviants. While overlap of N1 enhancement with the MMN is problematic in any study, it poses special risks in manipulations of deviant probability. Decreasing deviant probability may increase the degree of differential afferent activation between the standard and the deviant. As such, decreasing the probability of the deviant may increase the contribution of N1 enhancement to the difference wave, causing artificial enhancement of the MMN. Study 3 therefore examines the effect of deviant probability on the MMN using the two-tone alternating pattern. Because no differential effects of probability are expected to occur between small and large MMNs, the pattern was presented only with a 6 semitone separation between the two tones.

The 3 different approaches used in the present thesis, therefore, are designed to test the proposed weak automaticity of the MMN by using patterned auditory stimuli to study its susceptibility to attention, unconsciousness, and the strength of the memory for the standard.

Chapter 2:

The Influence of Strongly Focused Visual Attention on the Detection of Change in an Auditory Pattern

1. Introduction

The detection of acoustic change is critical for survival. This process of acoustic change detection is reflected by an event-related potential called the Mismatch Negativity (MMN). A large majority of studies record the "classic" MMN using the oddball task (see Näätänen et al., 2007 for a recent review). In the oddball task, the subject is presented with a sequence of discrete, homogeneous "standard" auditory stimuli. At rare and unpredictable times, a physical feature of the standard is changed producing a "deviant" stimulus. The standard elicits a complex known as the N1-P2 vertex potential. In addition to N1-P2, the deviant stimulus elicits the MMN. The MMN is best observed as a difference wave, computed by subtracting the standard from the deviant ERP. The subtraction process removes exogenous, sensory processing that is common to both the standard and the deviant, leaving only processing that is unique to the deviant (Näätänen et al., 1980).

The MMN peaks 100-250 ms after the onset of the deviant stimulus, with a larger extent of deviance eliciting a MMN with higher amplitude, and shorter latency (Näätänen et al., 1989). The MMN is maximal over frontocentral scalp cites, and inverts at the mastoids when the nose is used as reference (Näätänen et al., 1980). This scalp distribution has largely been explained by intra-cranial sources located in the supratemporal region of the auditory cortex (Alho, 1995). There may also be a contribution of a second source in the right frontal lobe, although it remains poorly understood (Giard et al., 1990; Rinne et al., 2000).

Almost any physical stimulus change will elicit the MMN, including tonal frequency (Näätänen et al., 1978; Sams, Paavilainen, et al., 1985), intensity (Näätänen et al., 1987), duration (Näätänen et al., 1989), and spatial location (Paavilainen et al., 1989). Complex deviants such as a change in speech sounds will also elicit the MMN (Winkler et al., 1999). The scalp distribution of the MMN varies depending on the type of deviant that is used (Alho, 1995).

The MMN occurs when the physical features of an incoming stimulus change from those that precede it. It can also be elicited by a violation of a complex regularity (Näätänen et al., 2001). The large majority of studies have employed a physical change to "first-order" standard stimulus features. In studies of the MMN to more complex and abstract changes, there may be no physically identical, repetitive standard stimuli. Rather, what is "standard" is a more abstract regularity that is shared by several physically different standard stimuli. For example, Tervaniemi et al. (1994) presented subjects with a sequence of continuously descending tones (each tone being lower in frequency than the preceding tone). Deviant stimuli either ascended, rather than descended, or repeated the same tone. Both types of deviants elicited the MMN.

The MMN has been elicited by violations of a variety of complex regularities (Paavilainen et al., 1999; Winkler and Schröger, 1995; Paavilainen et al., 2003; Tervaniemi et al., 1994; Sussman and Gumenyuk, 2005; Saarinen et al., 1992; Nordby et al., 1988b; Zachau et al., 2005). Alain and colleagues (1994) employed a simple alternating pattern of two paired tones (ABABAB). Deviant stimuli in this paradigm were repetitions of either the A or the B tone (eg. ABAABA). The two tones in the pair were separated by 1, 6, or 12 semitones, and pattern violations produced a MMN that increased in amplitude with increasing tonal separation.

Because the detection of acoustic change is critical for survival, it needs to occur rapidly, and without the need for active attention being directed towards the auditory channel. In the Näätänen model of auditory perception, change detection is claimed to occur prior to awareness that change has occurred (i.e. at a pre-conscious level). The MMN was originally conceptualized to be strongly automatic: it did not benefit from attention, and was not dependent on it. A large number of studies have tested this claim using the oddball paradigm. Early studies described the MMN to be unaffected by attention, since deviants in both the unattended and attended channels of a dichotic listening task appeared to elicit MMNs of equal amplitude (Näätänen et al., 1978; Näätänen et al., 1980; Alho et al., 1989; Alho et al., 1994). Later dichotic listening studies, using more optimal paradigms, demonstrated a smaller MMN to unattended than attended deviants (Woldorff et al., 1991; Woldorff et al., 1998; Arnott and Alain, 2002; Trejo et al., 1995). There are, however, methodological problems with intramodal studies of selective attention. The active detection of the rare auditory deviant (or "target") will elicit another negativity, the N2b, that peaks at about the same time and shares a similar frontocentral scalp topography with the MMN. Näätänen and colleagues (1993) have thus argued that the apparent enhancement of the MMN with attention directed to the auditory channel may, in fact, be a result of effects on the overlapping and summating N2b. The N2b does not invert in amplitude at the mastoids, whereas the MMN does, but this difference is quite subtle and is not always apparent in ERP recordings.

The problem of N2b overlap is overcome in many MMN studies by ensuring subjects do not attend to the auditory channel, and overtly detect the rarely-occurring deviant. Subjects are thus often engaged in an intermodal (visual-auditory) task, being asked to attend to a visual task and ignore the concurrent standard and deviant stimuli occurring in an incidental auditory channel. The ease of the visual task is often manipulated. The more difficult task is presumed to demand a greater focusing of attention. The underlying assumption in these studies is that the strong demands of a difficult visual task do not allow the subject to either rapidly switch or share resources between the visual task and task-irrelevant auditory stimuli. In contrast, it is assumed that during the easy visual task, subjects will have additional resources available for the processing of auditory stimuli. Most research using intermodal visual-auditory tasks have demonstrated the MMN to be unaffected by the visual task (Dyson et al., 2005; Dittmann-Balcar et al., 1999; Muller-Gass et al., 2006; Muller-Gass et al., 2007; Kathmann et al., 1999; Otten et al., 2000; Harmony et al., 2000; Alho et al., 1994; Sams, Paavilainen, et al., 1985; Sams et al., 1984). A small number of studies, particularly those in which a continuous visual task is employed, have reported effects of visual task difficulty on the MMN to a large frequency deviant in an oddball task (Kramer et al., 1995; Restuccia et al., 2005; Yucel et al., 2005; Zhang et al., 2006). The most recent Näätänen model (Näätänen et al., 2007) classifies the oddball MMN as a weakly automatic process: although the MMN is elicited independently of attention, attention may modulate its amplitude (see Hackley, 1993 for a discussion of this concept).

While the effects of attention on the MMN elicited by physical deviants in an oddball task have been widely studied, little is known about the effects of attention on the pattern MMN. Alain and Woods (1997) noted in a dichotic listening task that the pattern MMN was larger in the attended auditory channel than in the ignored channel. The problem of N2b overlap with the MMN during active attention, however, cannot be dismissed in these studies.

The present study employed an intermodal paradigm in which subjects were engaged in either an easy or a difficult visual task, and were asked to ignore concurrently presented auditory pattern stimuli. The use of a discrete visual task is problematic for the study of the pattern MMN. This is because discretely-presented stimuli become integrated into the auditory sequence, thus disrupting the pattern in which the auditory stimuli are presented. To avoid disruption of the auditory pattern, a continuous visual multiple object tracking (MOT) task was employed (Pylyshyn and Storm, 1988).

The MOT task was modified from the original Pylyshyn and Storm (1988) design to produce a tracking period of sufficient length for auditory pattern presentation. Subjects tracked circular targets among identical non-targets as they moved randomly across the screen. Visual probes, in the form of a color change, required a response if they occurred in one of the target objects. The purpose of this study was to investigate the susceptibility of the pattern MMN to the demands of this continuous visuospatial task. The difficulty of the visual task was manipulated by varying the number of objects to be tracked, and the number of non-target objects to be ignored. There is some evidence that MMNs elicited by smaller deviations may be more susceptible to the effects of attention (Muller-Gass et al., 2006; Näätänen et al., 1993). For this reason, two auditory conditions were used, in which the constituent tones of the auditory pattern were separated by either 1 or 6 semitones (Alain et al., 1994).

2. Results

2.1 *Performance Data*

Performance on the tracking task was assessed by hit rate (HR) and reaction time (RT). Both were tested by two-way ANOVAs with repeated measures on the factors Semitone (1 vs. 6 semitones) and Difficulty (Easy vs. Difficult). Accuracy (HR) was significantly affected by task demands, $F(1,13) = 42.80, p < 0.01$, with a mean HR of 0.91 (SD = 0.04) in the Easy condition, falling to 0.69 (SD = 0.11) in the Difficult condition. Conversely, RT was significantly prolonged in the Difficult task, $F(1,13) = 11.01, p < 0.01$, increasing from a mean of 717 ms (SD = 70 ms) to 808 ms (SD = 75 ms) from probe onset.

2.2 *ERP Data*

2.2.1 *6 Semitone Condition*

The left column of Figure 1 depicts the grand average standard and deviant waveforms in the reading task under the 6 semitone condition, using a 1000 ms epoch. The standard stimulus epochs contain numerous small deflections that likely represent obligatory processing of the 4 standard tones presented within the 1000 ms averaging period. The standard ERPs were essentially identical in both the 1 and 6 semitone conditions, and across the Easy, Difficult, and Reading tasks. In waveforms for the deviant stimuli, the obligatory processes are overlapped by large deviance-related negativities (DRNs) at 150 and 400 ms. Deviant minus standard difference waveforms are also illustrated in Figure 1. The early DRN (MMN) around 150 ms, a small positivity (P3a) around 250 ms, and a late DRN at 400 ms are isolated in the difference wave.

Figure 2 illustrates task effects in the 6 semitone condition. The mean amplitudes of the MMN, P3a, and DRN across conditions are summarized in Table 1. The MMN displayed a frontocentral maximum, and inverted in amplitude at the mastoids. It was quantified at frontal sites, where it was largest. A two-way ANOVA with repeated measures was run with the factors Task (Easy, Difficult, and Reading), and Electrode (Fz, F3, and F4). Greenhouse-Geisser corrections for violation of sphericity were applied to all ERP analyses, and epsilon values are reported. MMN amplitude varied significantly according to electrode site, $F(2,26) = 6.34, p < 0.05, \varepsilon = 0.66$. Tukey's post-hoc revealed this negativity to be larger at Fz than at F3 and F4. Amplitude of the MMN at F4 was larger than that at F3 but this difference was not significant. Importantly, there was no significant effect of the visual task on the MMN, $F < 1$. The MMN was not larger in the Easy than in the Difficult condition.

A small P3a (less than 1 μV) occurred at approximately 250 ms. It tended to be equally-distributed across Fz, Cz, and Pz. A significant electrode site by task interaction $F(4,52) = 3.85, p < 0.05, \varepsilon = 0.66$ was found. Tukey's post-hoc demonstrated this interaction to be caused by a larger amplitude at Pz in the Easy condition than in the Difficult condition. Task effects were not significant at other electrode sites.

A later negativity, DRN, peaking around 400 ms, exhibited a very similar distribution to the earlier MMN, having a frontocentral maximum and inversion over mastoid sites. This DRN was thus also analyzed at frontal (Fz, F3, F4) sites. Like MMN, the amplitude of the DRN was subject to a main effect of electrode site $F(2,26) = 5.41, p < 0.05, \varepsilon = 0.96$. Tukey's post-hoc revealed it to be larger at Fz than at F3. The mean amplitude at F4 was larger than F3, but again this did not reach significance. The effects of the visual task were not significant on this DRN, $F < 1$.

2.2.2 *1 Semitone Condition*

Figure 3 illustrates task effects in the 1 semitone condition. As in the 6 semitone condition, the MMN displayed a frontocentral maximum, and inverted in amplitude at the mastoids. At frontal sites, a repeated samples t-test showed the MMN in the 1 semitone condition to be significantly reduced compared to the 6 semitone condition $t(13) = 8.19, p < 0.01$. Just as in the 6 semitone condition, a two-way ANOVA with repeated measures on the factors Task (Easy, Difficult, and Reading), and Electrode (Fz, F3, and F4) was performed. The amplitude of the 1 semitone MMN varied significantly according to electrode site, $F(2,26) = 4.97, p < 0.05, \varepsilon = 0.96$. Tukey's post-hoc revealed this negativity to be larger at Fz than F3. Amplitude of the MMN at F4 was larger than that at F3 but the difference was not significant. Again, there was no significant effect of task on the MMN, $F(2,26) = 1.83$.

As in the 6 semitone condition, a small P3a (less than 1 μV) occurred around 250 ms. The amplitude of this P3a did not significantly differ between semitone conditions $t < 1$. A significant task by electrode site interaction was found, $F(2,26) = 2.76, p < 0.05$, but after application of the Greenhouse-Geisser correction, the interaction failed to reach significance $\varepsilon = 0.64, p = 0.07$. Follow-up testing was nevertheless performed, and revealed the P3a at both Cz and Pz to be larger in the Easy condition than in the Difficult condition ($p < 0.01$).

The DRN at 400 ms again inverted over mastoid sites. A repeated measures t-test showed the DRN to be larger in the 6 semitone condition than in the 1 semitone condition

$t(13) = 4.59, p < 0.01$. The DRN was uniformly distributed across Fz, F3, and F4. There was no significant effect of task, nor was there any significant interaction between task and electrode site ($F < 1$ in both cases).

3. Discussion

The performance data provide strong evidence that the Difficult continuous visual task did indeed require more attentional resources than the Easy task. RT was significantly longer and HR significantly lower during the Difficult MOT task. Very few resources should therefore have been available for the sampling of the auditory channel during the Difficult compared to the Easy visual task.

Deviations from the alternating tone pattern elicited a fronto-central MMN that inverted in amplitude at the mastoids. This MMN was larger at right than left frontal sites. Although the difference between the right and left frontal sites was not significant, this topography is similar to that reported by Alain et al. (1994). The semitone separation conditions successfully modulated the MMN, producing larger MMNs in the 6 semitone condition than in the 1 semitone condition. This also replicates the Alain et al. (1994) findings.

Importantly, the difficulty of the continuous visual task did not have any significant effect on the pattern MMN elicited in either the 1 or 6 semitone condition. Muller-Gass et al. (2007) employed a similar visual MOT task and also failed to find an effect of task demands on an MMN elicited by either an intensity increment or decrement in an auditory oddball sequence. They cautioned that although their task manipulation did result in a significant effect on task performance, the range of difficulty (about 10% decrement in accuracy and a 60 ms increase in RT during the Difficult task) might not have been large enough to have a significant effect on the MMN. The decrement in performance during the Difficult task was much wider in the present study (a 22% decrease in accuracy and a 91 ms increase in RT), yet the MMN remained unaffected by the manipulation of task demands. Moreover, the MMN elicited in the Reading condition did not significantly differ from those elicited during the Easy and Difficult MOT tasks.

Several studies have failed to find an effect of the task demands of a visual task on the auditory MMN when discrete visual stimuli are presented alongside an ignored auditory oddball sequence (see Muller-Gass et al., 2006 for a review). Such results are in line with the expectations of more recent models of attention and the MMN (Sussman, 2007). According to Sussman (2007), the effects of attention on MMN elicitation are primarily the result of its influence on formation of the representation of the standard, rather than modulation of the deviance detection mechanism itself. This model asserts that attention affects the deviance detection system only under very specific circumstances, such as when deviants in attended and ignored acoustic streams compete for processing resources. Varying the demands of a visual task should thus have little effect on the MMN, even if the visual task is exceedingly difficult.

Nevertheless, some intermodal studies using continuous visual tasks have demonstrated significant general effects of attention on the MMN (Kramer et al., 1995; Yucel et al., 2005; Restuccia et al., 2005; Zhang et al. 2006). Yucel et al. (2005) employed a task in which subjects were required to use a joystick-device to continuously track the movement of an object on a monitor. The MMN elicited by moderately large frequency deviants in a slowly presented oddball sequence was significantly reduced when the visuomotor task was made to be more difficult.

There is evidence that the MMN may consist of both temporal and frontal subcomponents (Giard et al., 1990). Some research suggests that the frontal MMN subcomponent is more likely than the temporal component to be modulated by attention, due to its role either as an attention-switch mechanism, or a contrast-enhancing mechanism that becomes engaged under conditions where deviance detection is more difficult (Deouell, 2007). Large frequency deviants, however, also elicit other negativities related to the activation of fresh afferent neuronal populations (Näätänen et al., 2007).

Recently, Zhang et al. (2006) employed a MOT task similar to that used in the present study while concurrently presenting 1000 and 1500 Hz standards and deviants, respectively. The MMN elicited by the frequency deviant was larger during the most difficult visual task. They reasoned that the difference in their results compared to others, like Yucel et al. (2005), is because the MOT manipulates working memory load, whereas other studies manipulated perceptual difficulty (Lavie et al., 2004). The MOT is an effortful task that requires the subject to maintain the positions of the moving targets in working memory (Oksama and Hyönä, 2004). The demands on working memory are higher when more objects need to be tracked. Since Zhang et al. (2006) also used large frequency deviants that elicit a composite negativity, the effects of the continuous MOT task on their DRN were also ambiguous.

An advantage to the use of an auditory pattern is that the deviant stimulus contains no new physical features. A simple alternating pattern served as the standard in the present study. A large MMN was elicited when the two tones in the pattern were separated by 6 semitones. This large MMN was elicited by a repetition of the same, physically identical stimulus. This large negativity cannot, therefore, be a result of the activation of fresh afferents. Both in this case, and in the case of the smaller MMN in the 1 semitone condition, the MMN was not affected by the number of objects to be tracked.

Subtle differences between the current paradigm and that used by Zhang and colleagues (2006) might also explain the conflicting results. Auditory stimuli were presented relatively slowly (every 600 ms) in Zhang et al., but relatively rapidly (every 250 ms) in the present study. Although both studies employed the MOT task, subjects were required to detect and immediately respond to color changes during object movement in the present study, while in Zhang et al., probe stimuli were presented at the end of each block. It is thus possible that the demands on working memory were different in the two studies. Of course, it is also possible that the demands of the MOT task affect the more bottom-up processing of the physical deviants in an oddball paradigm differently from the more top-down processing of rule-based deviants in a pattern paradigm.

A small positivity was elicited by the deviant stimuli. Its peak latency (about 250 ms) was similar to that of the P3a. However, its topography was more evenly distributed across the scalp than the usual centro-frontal P3a. The P3a is thought to reflect an involuntary attention switch from the task at hand to a distracting auditory event (Escera et al., 1998; 2000). The strength of the output of the change detector system, as reflected by the amplitude of the MMN, is considered to affect the generation and amplitude of the P3a. Thus, the P3a is large following the presentation of a large extent of stimulus change (Muller-Gass et al., 2006; Muller-Gass et al., 2007). In the present study, the MMN was much larger in the 6 than in the 1 semitone condition, yet the amplitude of the small late positivity did not significantly vary between the two semitone conditions. Alain et al.

(1994) did not report P3a activity, but it is apparent from their Figure 2 that even their largest MMNs were not followed by a P3a. Again, it is possible that the relationship between the more bottom-up, physically-driven MMN and P3a is different from that of the more top-down, rule-derived MMN and P3a.

In the 1 semitone condition, at Cz and Pz, the small P3a was nevertheless attenuated under conditions of high working memory load. Zhang et al. (2006), and Berti and Schröger (2003) also noted that P3a was attenuated when working memory load was increased. Such inhibition of the P3a under conditions of high memory load may be limited to conditions where the active task and the distractor occur in clearly separated channels (Muller-Gass and Schröger, 2007). The P3a elicited in the 6 semitone condition was also modulated by task difficulty, but only at the Pz scalp site. Again, it can be questioned whether this small positivity was, in fact, a true P3a.

A later DRN peaking at about 400 ms was also observed following presentation of the deviant. This DRN shared several properties with the MMN, including a frontocentral maximum, and inversion at the mastoids. In our stimulus sequence, the first standard immediately following the deviant (ABABABBBA) might also be perceived as a deviant, because it is a repetition of the previous stimulus. The timing of this DRN, at approximately 150 ms following the onset of this post-deviant standard, suggests that it is at least in part a MMN due to this perceived deviance. The DRN did however peak at 400 ms following onset of the real deviant. It may thus represent in part a reorienting negativity (RON), reorienting attention to the visual task following distraction (Schröger and Wolff, 1998). Determining whether the RON truly contributed to this DRN would require performance data examining whether deviant presentation affected RT or HR. It would be extremely difficult to implement such performance measures of distraction in this paradigm, due to potential confounds, such as auditory deviant presentation providing a cue for MOT probe onset. Although its exact origins are ambiguous, this late DRN was not affected by task difficulty.

In conclusion, the present study demonstrates that the MMN elicited by pattern violations is not affected by the difficulty of a continuous tracking task. These results conflict with previous studies showing the susceptibility of oddball deviant MMNs to task load. The disparity in these results may indicate that the MMN to rule violations is differently affected by visual task load than is the MMN to simple, physical deviations. Alternatively, the current study may provide a more valid test of MMN automaticity, given that studies demonstrating MMN modulation by visual task load employed large pitch deviants that might have activated fresh afferent neuronal populations. Although it did not display the typical P3a topography, a small positivity in the P3a latency range was elicited by the deviant stimuli, and was modulated by task demands. A later DRN was apparent 400 ms after deviant onset. Like the MMN, it was not modulated by task load. This DRN might represent a composite RON to the deviant and a MMN to the subsequent standard stimulus which might have been perceived as deviant.

4. Experimental Procedure

4.1 *Subjects*

Fourteen young adults (all female, aged 18-25 years), all with no history of neurological or hearing problems, volunteered to participate in the study. Written informed consent was obtained prior to the study, and participants received monetary honorarium as compensation. This study was carried out according to the Canadian Tri-

Counsel guidelines (Medical, Natural, and Social Sciences) on ethical conduct for research involving humans.

4.2 *Procedure*

4.2.1 *Auditory Stimuli*

Patterned auditory stimuli were presented during an active multiple object tracking (MOT) task but were irrelevant to it. Twenty-five second runs of auditory stimuli were embedded within the 30 s MOT trials such that auditory stimuli were only presented during the tracking portion of the MOT task. These 25 s auditory runs were followed by 10 s pauses.

The auditory pattern is illustrated in Figure 4. It consisted of two alternating 80 dB SPL pure tones (A and B), each having a duration of 100 ms, including a 10 ms rise/fall time. The onset-to-onset interstimulus interval (ISI) between these tones was held constant at 250 ms. The frequencies of these tones varied in two different conditions. In the 6 semitone separation condition, the A and B frequencies were 841 and 1189 Hz, while in the 1 semitone separation condition, they were 1000 and 1059 Hz, respectively. Similar stimuli were employed by Alain et al. in 1994. Deviants within this alternating standard pattern were a repetition of either the A or the B tone. Deviant repetitions had a probability of 0.0325, and occurred at random under the constraint that the time between deviant presentations varied between 4 and 20 s.

4.2.2 *Visual Task*

Subjects were seated in an acoustically shielded room, 50 cm from an LCD monitor. They were required to perform a visual MOT task, while ignoring the concurrently-presented auditory patterns. Two MOT conditions that varied in difficulty (Easy and Difficult) were administered, as well as one reading condition.

The MOT task is illustrated in Figure 5. It consisted of identical white balls (1 cm diameter; approx. 1.5° visual angle) that appeared within a 20×15 cm gray window at the beginning of each trial. The background behind this window was black. At the beginning of each trial, one or a number of these balls flashed to designate them as targets: solid balls were non-targets. The display then returned to its pre-task state, where targets and non-targets both appeared as identical white balls. The balls then proceeded to move in random directions around the monitor, their motion subject to random Brownian-like variation that produced unpredictable horizontal and vertical paths. The circles moved smoothly at a constant 6°/s velocity. Colliding objects were allowed to slide through one another, but bounced off of the edges of the window.

At random times, at least 3 s apart, and on average every 5 s, any of the objects could change color from white to black (or perhaps black to white if the object had previously turned black). This color change served as a probe, and if it took place in a target object, participants were required to respond by button press. No response was required if the color change took place in a non-target object. This MOT block had a 30 s duration, and participants were given a 5 s pause before commencing a new block. Each task condition lasted 12.5 minutes, and contained 24 MOT blocks. Each MOT block contained 100 auditory stimuli, for a total of 2400 auditory stimuli per task condition.

At the beginning of the session, each subject was given a 4 min practice run of the MOT task with 2 targets and 2 non-targets. Auditory stimuli were not presented during this practice condition.

In the Easy condition, subjects were required to track 1 target in the presence of 1 non-target. In the Difficult condition, subjects began with 2 targets and 2 non-targets. If their performance on any block improved to above an 0.80 hit rate, the Difficult condition was increased to 3 targets and 3 non-targets. The change to the 3 targets/non-targets condition occurred for all but one subject, usually after experience with 2-3 Difficult task conditions.

In a separate Reading condition, participants were asked to read a book and ignore the auditory stimuli. Reading tasks, or similar "ignore" conditions such as watching a silent movie, are often used in MMN research. The MMN in the Reading task was thus used as a baseline condition to be compared to those recorded during the MOT task. All 6 conditions (3 visual tasks × 2 auditory tone separations) were presented twice during the recording session. The order of presentation of the 12 conditions was randomized.

4.3 *Data Acquisition and Analysis*

The EEG was recorded from 10 scalp sites of the 10-20 system, including Fz, F3, F4, Cz, Pz, P3, P4, T7, T8, and Oz, using tin electrodes mounted in an elasticized cap (ElectroCap International Inc., Eaton, OH). Two additional tin electrodes were placed at the left and right mastoids (M1, M2). The nose was used as reference for all sites. A vertical EOG was recorded from the supra- and infra-orbital ridges of the left eye, and a horizontal EOG was also recorded with electrodes placed at the outer canthus of each eye. Impedance at all electrode sites was reduced to below 5 kΩ.

The EEG and EOG signals were sampled at a rate of 256 Hz, with a 2 s time constant and a high filter set to 35 Hz, and stored for offline analyses. Eye movement and blink artifact were corrected using an algorithm operating in the time and frequency domains (Woestenburg et al., 1983). The continuous EEG was baseline corrected and then subsequently reconstructed into discrete 700 ms epochs including a 100 ms pre-stimulus baseline. Any trials containing EEG changes exceeding ±100 μV were rejected from averaging. The single trials were sorted and averaged on the basis of stimulus type (standard or deviant), semitone condition (1 or 6 semitone separation), and task condition (Easy MOT, Difficult MOT, or Reading). The resulting averages were digitally filtered using an inverted FFT algorithm with a low-pass filter of 20 Hz, and a high-pass filter of 0.8 Hz. All deviants, regardless of whether they were low or high tones (repetitions of A or B), were averaged together, as were all standards. The first 4 standard stimuli of each auditory run, as well as the 4 standards following each deviant were excluded from averaging.

The 100 ms pre-stimulus interval served as a baseline from which the ERPs were scored. Amplitudes for the MMN, and P3a components were measured in the difference wave computed by subtracting point-by-point the auditory standard from the deviant ERPs at each electrode site. MMN and P3a amplitudes were computed as the average of all data points were taken in the ±20 ms period surrounding peak deflections identified in the grand average. A later negativity peaking at about 400 ms was also apparent in the difference wave. This "deviance-related negativity" (DRN) was also quantified as the average of the ±20 ms period surrounding peak deflections identified in the grand average.

Figure Caption

Figure 1: ERP deflections to standard and deviant stimuli during the Reading task in the 6 and 1 semitone conditions. Note numerous deflections in the standard stimulus response, due to overlapping obligatory ERPs to the 4 stimuli presented within the 1000 ms averaging epoch. These small potentials are overlapped by large MMN processes that are isolated in the deviant-standard difference waves. Two negativities are apparent in the difference waves, a MMN at 150 ms, and a later DRN at 400 ms. Both invert in polarity at the mastoids.

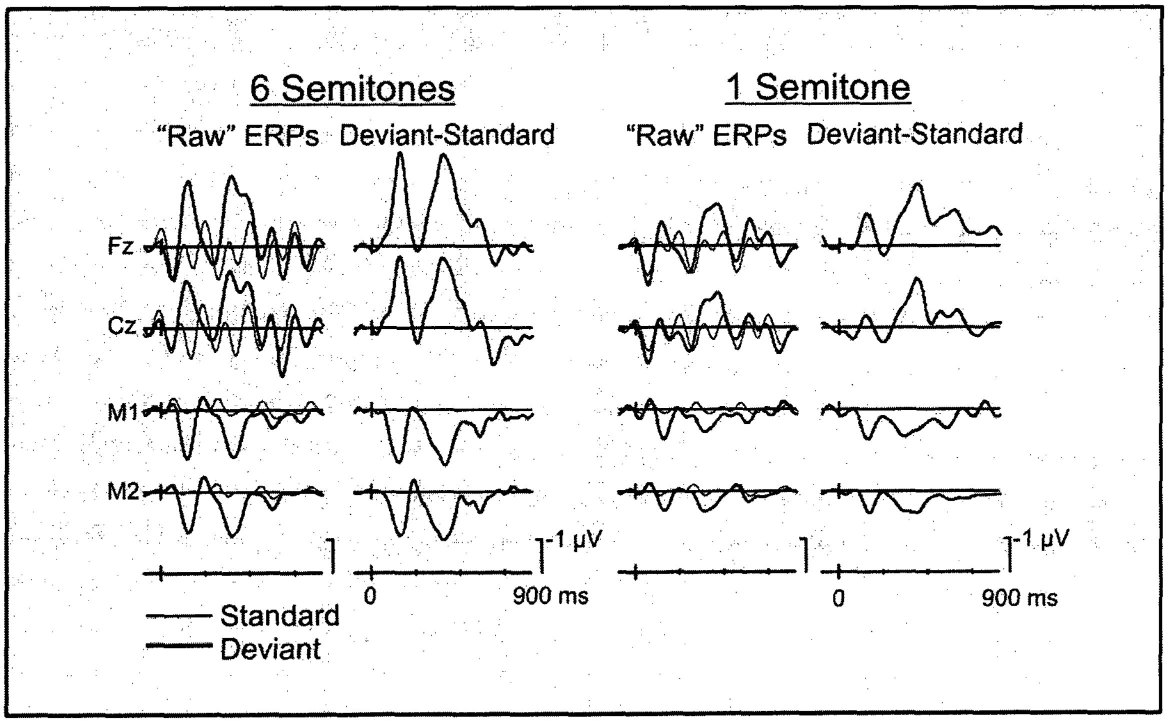

Figure Caption

Figure 2: Grand average difference waves in the 6 semitone condition. A large amplitude, fronto-central MMN is apparent at about 150 ms. This MMN did not vary between the Difficult and Easy MOT conditions, nor was it different in the Reading task. A small amplitude P3a peaking at about 250 ms is also apparent. This is followed by a large DRN peaking at about 400 ms. This DRN was not significantly influenced by task demands.

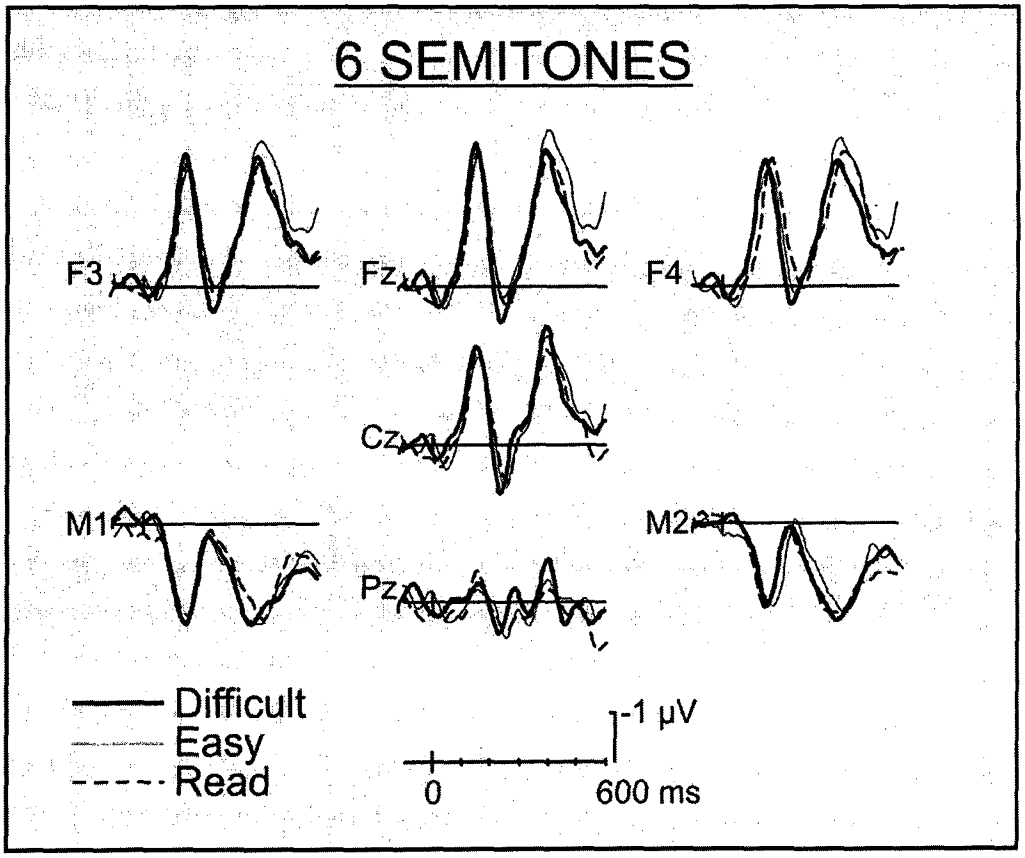

Figure Caption

Figure 3: Grand average difference waves in the 1 semitone condition. A smaller amplitude MMN was elicited at about 150 ms. This MMN was not influenced by task demands, nor was a later (400 ms) DRN. A small P3a was again elicited around 250 ms. It was significantly larger in the Easy compared to the Difficult MOT task at Cz and Pz.

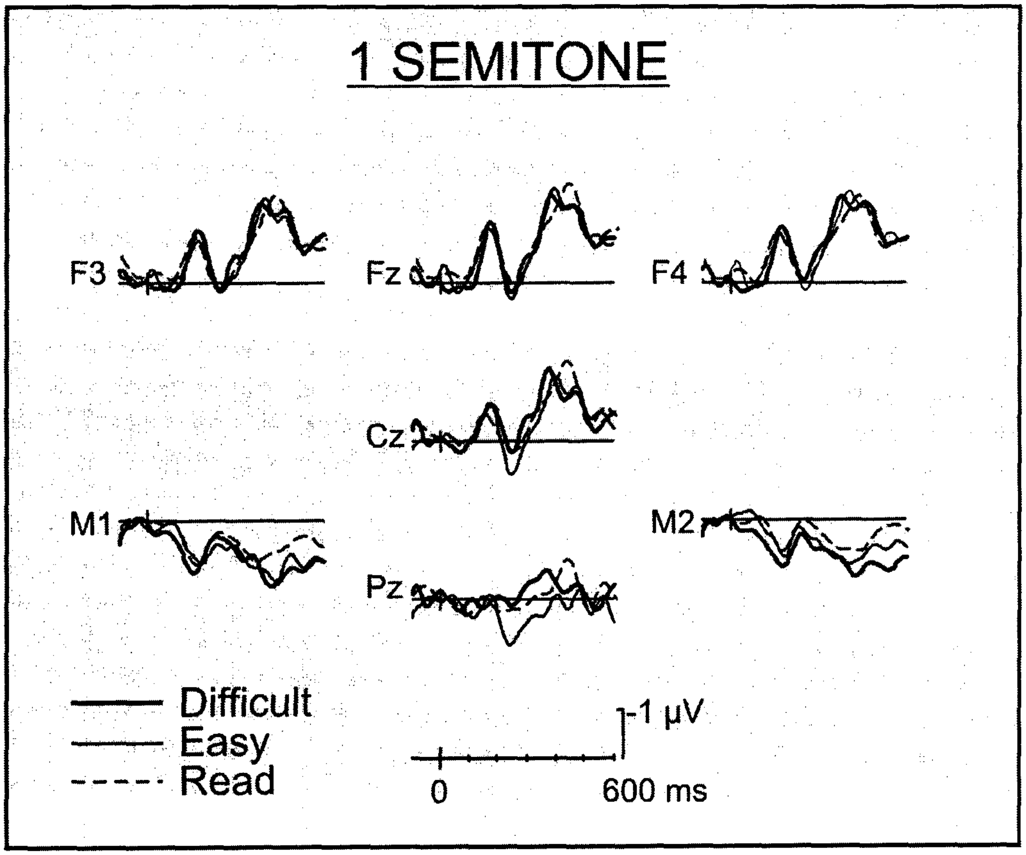

Figure Caption

Figure 4: An illustration of the auditory pattern, consisting of low (A) and high (B) tones that were either separated by 1 or 6 semitones in different conditions. Frequencies in these conditions were 1000 and 1059 Hz, and 841 and 1189 Hz, respectively. Deviants violated the alternating pattern by repeating either the A or the B tone. These deviants occurred at random, under the constraint that successive deviants were no less than 4 s and no more than 20 s apart. Note that the first standard tone following the deviant is also a repetition, and therefore may have been considered "deviant" by the change detection system.

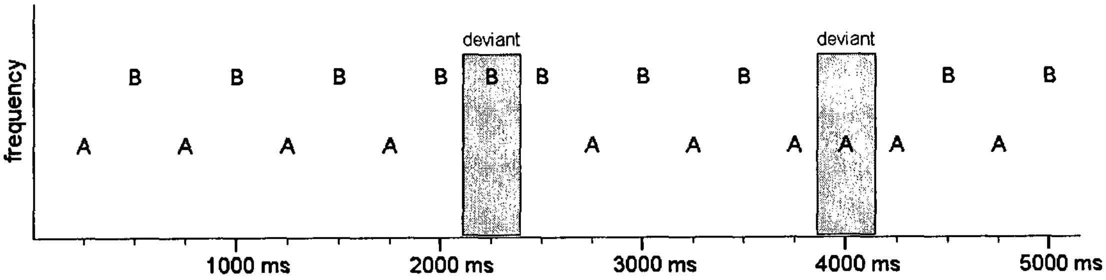

Figure Caption

Figure 5: An illustration of the MOT task, Difficult condition. a) The task begins, all stimuli are identical. b) Target stimuli are identified by flashing. c) Tracking is about to begin. All stimuli are identical. d) Stimuli have been moving randomly and a color change serves as a probe. Subjects respond by button press if the probe is in a target object. In this example, the subject should respond.

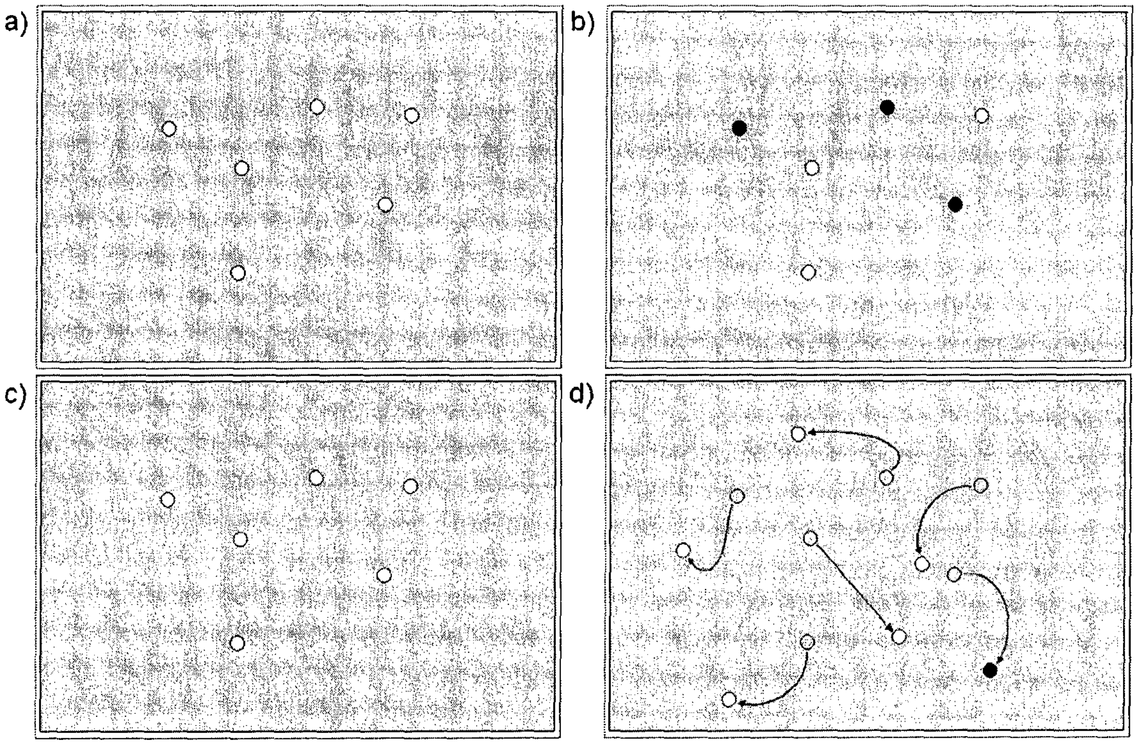

Table 1: Means and standard errors of the means (in parentheses) for MMN, P3a, and DRN amplitudes in the Easy MOT, Difficult MOT, and Reading conditions.

Condition	**MMN**			**P3a**			**DRN**		
	F3	Fz	F4	Fz	Cz	Pz	F3	Fz	F4
6 semitones									
Easy MOT	-2.04	-2.38	-2.22	0.38	0.70	0.36	-2.36	-2.65	-2.56
	(0.32)	*(0.31)*	*(0.30)*	*(0.34)*	*(0.35)*	*(0.30)*	*(0.28)*	*(0.29)*	*(0.24)*
Difficult MOT	-2.24	-2.63	-2.25	0.47	0.44	-0.15	-2.33	-2.60	-2.33
	(0.43)	*(0.46)*	*(0.42)*	*(0.34)*	*(0.34)*	*(0.27)*	*(0.34)*	*(0.35)*	*(0.33)*
Reading	-2.14	-2.43	-2.21	0.44	0.50	0.12	-2.19	-2.46	-2.35
	(0.33)	*(0.34)*	*(0.32)*	*(0.35)*	*(0.34)*	*(0.39)*	*(0.26)*	*(0.31)*	*(0.21)*
1 semitone									
Easy MOT	-0.65	-0.82	-0.81	0.40	0.64	0.66	-1.38	-1.49	-1.36
	(0.28)	*(0.28)*	*(0.24)*	*(0.22)*	*(0.24)*	*(0.22)*	*(0.24)*	*(0.23)*	*(0.21)*
Difficult MOT	-0.97	-1.13	-1.0	0.12	0.04	-0.02	-1.35	-1.53	-1.43
	(0.23)	*(0.26)*	*(0.22)*	*(0.30)*	*(0.32)*	*(0.27)*	*(0.29)*	*(0.33)*	*(0.31)*
Reading	-0.46	-0.63	-0.59	0.41	0.23	0.00	-1.12	-1.19	-1.09
	(0.24)	*(0.26)*	*(0.26)*	*(0.20)*	*(0.32)*	*(0.30)*	*(0.22)*	*(0.25)*	*(0.24)*

Chapter 3:

MMN Elicitation in Natural Sleep.

1. Introduction

The ability to detect changes in the environment that occur outside the realm of active focus is crucial for survival. Näätänen (1990) proposed a model of attention and automaticity in auditory processing in which two passive routes of processing have the potential to interrupt the limited-capacity central executive. This interruption allows the output of passive analysis to become available for further detailed analysis in the perceptual and cognitive systems, presumably requiring some form of conscious awareness. One route, associated with the N1 ERP component, detects obtrusive changes in the transient energy of stimuli, such as their onsets and offsets. A second route, associated with the mismatch negativity (MMN) ERP component, detects deviations from an otherwise homogeneous train of stimuli. The present study examines this second route to awareness.

The MMN exhibits a fronto-central maximum scalp distribution, peaks 100-250 ms following the onset of the deviant stimulus, and inverts in polarity over the mastoids when a nose reference is used (Sams, Hämäläinen, et al., 1985). Fundamental to the Näätänen model is the claim that the detection of change, signaled by the MMN, occurs whether the subject attends to the auditory stimuli or not. In other words, Näätänen's original model assumes that MMN generation occurs at a pre-attentive (or pre-conscious) level.

A number of studies have tested this assertion by examining the susceptibility of the MMN to manipulations of attention and task demands (for a recent review, see Sussman, 2007). Many intramodal studies (attend to one auditory channel, ignore another) have demonstrated a reduced MMN to deviant stimuli occurring in the unattended auditory channel, compared to when the same channel was attended (e.g. Woldorff et al., 1991; Trejo et al., 1995; Alain & Woods, 1997; Woldorff et al., 1998; Arnott & Alain, 2002; Alain & Izenberg, 2003). One criticism of intramodal studies of attention and the MMN is that overt attention to the stimuli in one channel elicits another negativity, the N2b, in addition to the MMN (Näätänen, et al., 1993). The N2b peaks about 250-300 ms after stimulus onset, and shares a similar fronto-central distribution with the MMN. The N2b does not, however, invert at the mastoids. Some manipulations yield an N2b that appears as a distinct peak (e.g., Sams et al., 1984; Sams, Paavilainen, et al., 1985), but the differences between the N2b and the MMN are often quite subtle. Several studies have nevertheless demonstrated attenuation of the MMN using procedures that minimized the possibility of measuring an overlapping N2b (Alain & Woods, 1997; Woldorff et al., 1998; Alain & Izenberg, 2003).

The N2b confound can also be overcome by requiring subjects to engage in a task in a different modality (usually visual) while ignoring the concurrently presented auditory stimuli[1]. In these intermodal paradigms, the difficulty of the visual task is often manipulated with the assumption that an easy visual task requires fewer attentional resources for its successful completion than a difficult one. Thus, during an easy visual

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[1] Even deviant stimuli in an ignored auditory channel can elicit the N2b, if the extent of deviance is quite large. The N2b elicited under these conditions has been attributed to a covert attention switch (Näätänen et al., 1982).

task, more resources would presumably be available to sample (or "eavesdrop" on) the to-be-ignored auditory channel, compared to a difficult task. Most studies have shown the MMN to be unaffected by the visual task (Alho et al., 1994; Dittmann-Balcar et al., 1999; Dyson et al., 2005; Harmony et al., 2000; Kathmann et al., 1999; Muller-Gass et al., 2005, 2006, 2007; Otten et al., 2000; Sams et al., 1984; Sams et al., 1985b; Sculthorpe et al., 2008), though not all have (Kramer et al., 1995; Yucel et al., 2005; Restuccia et al., 2005; Zhang et al., 2006).

Muller-Gass et al. (2006) questioned the underlying assumption of intermodal studies that subjects cannot sample the auditory channel during a difficult visual task. They thus employed both a focused condition, in which subjects actively performed a visual-perceptual task and ignored the auditory stimuli, and a divided attention condition, in which subjects were instructed to divide their attention and perform the visual task while also responding to targets in the auditory oddball sequence. Subjects were capable of successfully dividing their attention between the two tasks. Performance on the visual task declined slightly during the divided compared to the focused attention condition. Importantly, their ability to detect auditory targets was not modulated by visual task difficulty. This suggests that it is possible for subjects to covertly sample the auditory channel while performing a visual task, even if that task is very difficult. This might explain why many intermodal studies have shown the MMN to be unaffected by visual task difficulty.

Since both intramodal and intermodal studies run the risk that subjects might be covertly monitoring stimuli in a "to-be-ignored" channel, the best test for theories that claim certain aspects of processing are carried out independently of conscious awareness may be whether this processing can be demonstrated in unconscious state. A number of researchers have therefore examined the effects of natural sleep on the MMN. Sleep is associated with methodological problems that are different from those in the waking state. Sleep is not uniform. It consists of a series of stages, including non-REM (NREM) stages 1-4, reflecting the depth of sleep[2], and REM sleep. The amplitude of the background EEG is much higher during sleep than in the waking state, particularly during N3 (often > 200 μV). This can make the MMN (often < 1 μV) difficult to observe (Sabri & Campbell, 2002).

Most studies have failed to demonstrate an MMN in stage 2 of NREM sleep (Loewy et al., 1996; Nashida et al., 2000; Nielsen-Bohlman et al., 1991; Nittono et al., 2001; Paavilainen et al., 1987; Sallinen et al., 1997; Winter et al., 1995). Those that have done so used very large deviants (Sabri et al., 2000, 2003; Sabri & Campbell, 2005; Sallinen et al., 1994; Ruby et al., 2008). There is some evidence of an MMN in stage 3 (Ruby et al., 2008), but it cannot be elicited in stage 4 sleep. Unlike NREM, the MMN is very consistently reported in REM sleep, often with an attenuated amplitude compared to the waking state (Atienza & Cantero, 2001; Atienza et al., 1997, 2000; Loewy et al., 1996; Nashida et al., 2000; Ruby et al., 2008; Sabri et al., 2005).

There exist, however, methodological problems with much of the existing sleep MMN literature. These problems are primarily a consequence of the so-called “oddball” paradigm. In the oddball paradigm, the subject is presented with a sequence of discrete, identical standard auditory stimuli. At rare and unpredictable times, a physical feature is

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[2] In the recent 2007 American Academy of Sleep Medicine reclassification system, stages 1-4 are now labelled N1-N3, with N3 reflecting the combined stages 3 and 4.

changed to form a "deviant" stimulus that elicits the MMN. A change in any physical feature of the standard stimulus can elicit a MMN, including its tonal frequency (Näätänen et al., 1978; Sams, Paavilainen, et al., 1985), intensity (Näätänen et al., 1987), duration (Näätänen et al., 1989), or spatial location (Paavilainen et al., 1989).

Every investigation of the MMN to frequency deviants in sleep has used oddball paradigms, usually with frequency deviants (Atienza & Cantero, 2001; Atienza et al., 1997, 2000; Campbell et al., 1992; Loewy et al., 1996; Nashida et al., 2000; Nielsen-Bohlman et al., 1991; Nittono et al., 2001; Paavilainen et al., 1987; Sabri et al., 2005; Sabri et al., 2000, 2003; Sallinen et al., 1994, 1997; Winter et al., 1995).The frequency oddball paradigm may not elicit a pure MMN, particularly when the extent of deviance is large (Jacobsen & Schröger, 2001). Auditory afferent processing occurs in a tonotopic fashion, in which populations of sensory neurons are maximally responsive to specific tonal frequencies. In a frequency oddball paradigm, afferent activation by the often-presented standard pitch rapidly diminishes because neurons in the responsive population enter their refractory period. Deviants that are very different from the standards activate a different neuronal population. Since these deviants are rarely presented, the neuronal population responsive to the deviant pitch remains "fresh" and produces a large response when activated.

The N1 ERP component is much affected by the refractoriness of afferent neuronal populations, and its amplitude increases as the rate of stimulus presentation is slowed (Näätänen & Picton, 1987). The use of a frequency oddball paradigm therefore elicits a deviance-related negativity (DRN) that is composed of the superimposition of the MMN and the N1. Since the scalp-recorded N1 can overlap both spatially and temporally with the MMN, the separation of its contribution to the resultant DRN is often very difficult. The problem of fresh afferent activation remains a concern during sleep. N1 is reduced to baseline level during NREM sleep, but returns to 25-50% of its waking amplitude during REM sleep (Colrain & Campbell, 2007).

Few sleep studies have examined the MMN using paradigms that avoid N1 enhancement. Oddball sequences in which the deviants are created by decreasing stimulus intensity appear to be free of N1 enhancement (Jacobsen et al., 2003), but no MMN has been demonstrated to such stimuli during sleep (Loewy et al., 2000; Macdonald et al., 2008). Oddball sequences using deviants that have a shorter duration than the standard also appear to elicit a pure MMN (Jacobsen & Schröger, 2003). Duration decrement deviants have been reported to elicit the MMN in all stages of sleep, except stage 4 (Ruby et al., 2008). The same group has even reported MMNs to duration decrement deviants in comatose patients (Fischer et al., 1999). Thus, a definitive MMN has only been demonstrated in sleep using duration decrement deviants, and it is not known whether an MMN can be elicited in sleep by deviance along other stimulus dimensions.

Some sleep studies using frequency oddball paradigms attempted to minimize the risk of N1 overlap by using a small deviant (Loewy et al., 1996), or by using a deviant that represented a change to a complex standard stimulus that could only be detected after training (Atienza and Cantero, 2001)[3]. Both of these studies demonstrated the MMN during REM sleep, but the possibility of N1 enhancement cannot be discounted.

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[3] Atienza & Cantero used a variation of the oddball paradigm in which the standard and deviant stimuli were spectro-temporally complex units composed of 8 pure tones of 50 ms duration. Although these stimuli

The MMN is not restricted to the oddball paradigm. It can also be elicited by a violation of a complex regularity (Näätänen et al., 2001). In these paradigms, no physically identical standard stimuli exist. What becomes "standard" is a more psychological rule, or regularity, that governs the relationships among physically different standard stimuli. Deviants in these paradigms are rule violations. Nordby and colleagues (1988b) developed a simple rule violation paradigm using two alternating tones. In this paradigm, two tones of different pitch, A and B, consistently alternate in a standard pattern (ABABABAB…) that is occasionally broken by a deviant repetition (ABABAAB… or ABABBAB…). The deviant repetition elicits an MMN because it violates rules that have been extrapolated from the standard sequence based on the temporal organization of its two constituent tonal frequencies (Horváth et al., 2001). Since deviant stimuli in this paradigm are physically identical to the standard tones that precede them, the MMN cannot be attributed fresh afferent activation.

The MMN elicited by violations of such two-tone alternating patterns generally exhibits the same morphology as that elicited in the oddball paradigm. It possesses a peak latency in the 100-250 ms range, a maximum amplitude at fronto-central sites, and inverts at the mastoid when a nose reference is used (e.g., Alain et al., 1994; Takegata et al., 2005; Sculthorpe et al., 2008; Sculthorpe, Stelmack & Campbell, 2009). Mastoid inversion for the MMN to violations of an alternating pattern, however, does not appear to be as robust as that elicited by simple feature deviants in an oddball paradigm. While an intermodal study of attention demonstrated a mastoid inversion even during a very

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were complex in nature, they were still presented as an oddball sequence with identical standards. Deviants entailed a large frequency change in 1 of the 8 tones composing their complex stimulus units.

difficult visual task (Sculthorpe et al., 2008), an intramodal dichotic listening study demonstrated a small MMN to pattern violations in the unattended ear that did not invert in polarity at the mastoids (Alain & Woods, 1997).

The present study will employ a similar two tone alternating pattern to test for the presence of an MMN in natural sleep. The demonstration of an MMN in sleep to violations of an alternating pattern would not only provide convincing evidence of a true MMN to frequency-related deviance at the pre-conscious level, but would also indicate that the auditory system is capable of extracting more abstract rule violations even in an unconscious sleeping state.

Some studies employing the frequency oddball in sleep have also examined the effect of extent of deviance (Loewy et al., 1996; Sabri et al., 2000, 2003; Sabri & Campbell, 2005). Under these conditions, the MMN to large deviants was typically better preserved in sleep. The current study therefore employs two conditions, in which the constituent tones of the alternating pattern are separated by either 1 or 6 semitones. Unlike in frequency oddball paradigms, this increased tonal separation does not represent an increased "extent of deviance", as tonal frequency is not the dimension upon which deviance is established. Like the frequency oddball, however, MMN amplitude does appear to increase with tonal separation, probably due to increased perceptibility of the pattern (Alain et al., 1994). In the waking state, it was expected that the MMN in the 6 semitone condition would be larger than that in the 1 semitone condition. These patterned auditory sequences were also presented during a single night of natural sleep.

2. Results

2.1 *6 Semitone Condition*

The upper portion of Figure 1 illustrates the grand average standard and deviant "raw" ERPs in the 6 semitone condition across waking, NREM, and REM states. Standard tones elicited a small amplitude N1-P2 vertex potential, with N1 peaking at about 100 ms, and P2 visible at about 170 ms in the waking state (left column). The difference in processing (deviant minus standard ERPs) is illustrated in the bottom portion of the figure. The mean of all data points within consecutive 50 ms intervals of the difference waves are presented in Table 1 for Fz. In the waking state, a small positivity was present in the difference wave at about 80 ms that reached significance in the 50-100 ms interval. Following this positivity was a DRN that peaked at about 180 ms, and inverted at M1. This DRN was confirmed by a significant negative difference from baseline in the 150-200 ms interval at Fz, and a significant positive difference from baseline in the same interval at M1. The DRN in the waking state, therefore, appears to represent an MMN. In the waking state, the MMN was followed by a deflection that was significantly more positive-going than the baseline in the 250-300 ms interval. This positivity is probably a P3a.

During NREM sleep (middle column), near-baseline standard N1and P2 components were observed peaking at about 140 ms and 200 ms, respectively. In the difference wave (middle column), an early negativity peaked at approximately 90 ms. This negativity did not invert at the mastoid, and was followed by a positive deflection that peaked around 230 ms. None of the mean amplitudes in the eight 50 ms intervals, including those that contained the early negativity and positivity, significantly differed in amplitude from baseline.

During REM sleep (right column), a small N1-P2 was again observed. In the difference wave, a DRN peaking at 210 ms was apparent, and was significantly different from baseline in the 150-250 ms interval at Fz. At M1, a small positive-going deflection was apparent at the same latency as the DRN, but none of the mean amplitudes in the eight 50 ms intervals were significantly different from baseline. A repeated measures *t*-test was run to compare the amplitude of the MMN in the waking state to the DRN obtained in REM sleep. The *t*-test was carried out on the mean amplitudes in ±20 ms windows surrounding the peaks identified in the grand averages. Although the amplitude of the DRN in REM sleep was 12% smaller than the MMN obtained in the waking state, this difference was not significant ($t < 1$). The DRN observed during REM sleep was not followed by a significant positivity (P3a) in any of the subsequent intervals.

2.2 *1 Semitone Condition*

The upper portion of Figure 2 illustrates standard and deviant ERPs in the 1 semitone condition, across all states. The mean amplitudes for all intervals are summarized in Table 1. ERPs in the waking state (left column) were characterized by a very small N1 around 110 ms, and a P2 at 160 ms. Difference waves are illustrated in the bottom portion of Figure 2. The difference waveform consisted of a double-peaked DRN. These peaks are referred to as DRN1 and DRN2. The earlier peak, DRN1, peaked at about 110 ms, and was significant at Fz in the 100-150 ms interval, but did not invert in polarity at the mastoid. The later DRN2 peaked at about 205 ms at Fz, but was not significantly different from baseline. This negativity demonstrated an inversion at M1 that crossed baseline, but did not reach significance. Since DRN2 possessed both a frontal negativity and a mastoid inversion in the expected MMN latency, it was considered to be a "true" MMN. Because this MMN peaked at 205 ms, it is quite possible that the inclusion of data points relatively far in time from the actual peak smeared the mean amplitude. Confidence intervals were thus run on a window ±20 ms around the 205 ms peak. It, however, just failed to attain significance ($p < .08$). The mean amplitude of this MMN was 25% smaller than that elicited in the 6 semitone condition, but this difference was not tested because the MMN in the 1 semitone condition was not significantly different from baseline. No P3a was observed in the 1 semitone condition.

During NREM sleep (middle column), the N1 and P2 responses were at baseline level. None of the mean amplitudes computed in the 50 ms windows of the difference wave were significantly different from baseline. During REM sleep (right column), a small N1-P2 vertex potential was again apparent. As in NREM, none of the mean amplitudes computed in the 50 ms windows of the difference wave were significantly different from baseline.

3. Discussion

3.1 *ERPs in the Waking State*

During the waking state, a MMN was elicited in the 6 semitone condition which was significant both at Fz and at M1. This MMN was preceded by a small, significant positivity that peaked at about 80 ms. Similar small positivities are not unusual in the difference waves obtained to violations of an alternating pattern, using comparable rates of presentation (e.g. Nordby et al., 1988b; Alain et al., 1994; Takegata et al., 2005; Sculthorpe, Stelmack, et al., 2009). While the source of this positivity is unlikely to be P1 enhancement in response to the deviant repetition, it is well established that such repetitions diminish the amplitude of the N1 response (Butler, 1968). It is possible that the reduction of an overlapping negativity appeared as a positivity in the difference wave. Given that the N1 has been shown to decrease in amplitude as arousal declines in the sleep onset period (Campbell & Colrain, 2002), it is possible that drowsiness also contributed to this effect.

An MMN also appeared to be present in the 1 semitone condition in the waking state. This MMN did not reach significance, but was consistent with the typical morphology of the MMN, including a frontal negativity peaking in the 100-250 ms latency range and a concomitant polarity inversion at the mastoid. The MMNs that were recorded in the waking state in the present study are somewhat smaller relative to those observed by Sculthorpe, Stelmack, and Campbell (2009) and Alain et al. (1994) using similar patterns and the same rate of stimulus presentation. Drowsiness might account for these differences. The waking condition was recorded late at night, just prior to sleep. Some studies have shown the oddball MMN to be attenuated under conditions of sleepiness (Sallinen & Lyytinen, 1997) or drowsiness transitioning into sleep (Nashida et al., 2000). In summary, the waking MMNs of the present study are fairly consistent with the existing literature established using patterned stimuli in awake, alert subjects. Many of the differences from the established literature may be a consequence of drowsiness.

The MMN recorded in the 1 semitone condition during wakefulness was also preceded by a small negativity that was significantly different from baseline. In paradigms using very similar alternating frequency patterns at similar rates of stimulus presentation, a smaller frequency separation between the two tones of the pattern has been associated with a smaller, more complex MMN to pattern violations (Alain et al., 1994; Sculthorpe, Stelmack, et al., 2009). As mentioned previously, stimulus repetitions result in attenuation (not enhancement) of the N1. It is thus unlikely that this negativity represents an effect on the N1 component. It remains possible that this small negativity reflects an early component of the MMN response. It would be surprising, however, for the MMN to occur earlier to less perceptible deviants (deviants in the 1 semitone condition).

A relatively large P3a was apparent in the 6 semitone waking condition. Other studies using similar stimuli have not consistently demonstrated the P3a to pattern violations (Alain et al., 1997; Sculthorpe et al., 2008; Sculthorpe, Stelmack, et al., 2009). The occurrence of a relatively large P3a in the present study might also be a result of drowsiness. Sabri et al. (2000) also reported a P3a during the sleep onset period. This P3a was larger in relaxed wakefulness and stage 1 sleep than when the subject's EEG was indicative of "alert" wakefulness. The presence of a P3a has been suggested to reflect the interruption of the central executive and the subsequent switching of attention to the auditory channel (Escera et al., 1998). A deviant stimulus may thus disrupt the sleep onset process.

3.2 *ERPs in Sleep*

In the 6 semitone condition, a DRN was present in REM, but not in NREM sleep. This is consistent with many studies that used frequency oddball paradigms (Atienza & Cantero, 2001; Atienza et al., 1997, 2000; Loewy et al., 1996; Nashida et al., 2000; Sabri et al., 2005). The frequency deviants used in these studies may, however, have activated fresh afferents and as such the DRN may reflect the composite activation of both N1 and

MMN sources. The deviant in the present study was created by a repetition of the same physical stimulus, thus avoiding activation of fresh afferents. The DRN that was elicited therefore was unlikely to reflect activation of N1 sources.

The DRN observed in REM in the present study was attenuated relative to the MMN observed in the waking state, but this difference was not significant. Again, this result is very similar to previous studies that have reported a DRN to frequency deviants in REM sleep. Ruby et al. (2008), however, demonstrated a significant difference in MMN amplitude between the waking state and REM sleep, using a duration decrement deviant that should have avoided the N1 confound.

Does the REM sleep DRN in the present study truly reflect an MMN? As mentioned, the use of a pattern paradigm in which deviance was established by a repetition avoids the confound of fresh afferent activation. Nevertheless, the amplitude of the usual MMN polarity inversion at the mastoid was not significant. A positive-going deflection was however apparent. Alain and Woods (1997) reported an MMN that did not invert at the mastoid to pattern violation deviants presented to the unattended ear in a demanding dichotic listening task. Thus, when consciousness is inhibited, either by highly focused attention (Alain & Woods, 1997), or by a state of unconsciousness (the present study), it is possible that slightly different neural sources are activated in response to violations of an auditory pattern.

Alternately, the brain regions involved in auditory processing might be different in waking and sleeping states. Velluti (2008) has proposed a neuronal network/cell assembly model in which neuronal groups that subserve a specific function in wakefulness may become associated with different neural networks as part of the transition to sleep. Thus, some of the neuronal populations involved in generating the MMN in the waking state might remain active in the sleeping state, although they may form part of a slightly different neuronal network. The finding of only a small amplitude inversion at the mastoids is not unique to violations of a stimulus pattern. In sleep studies using oddball paradigms designed to prevent or minimize N1 overlap, the amplitude of the MMN inversion at the mastoid during REM sleep was either very small (Ruby et al., 2008), or near baseline (Loewy et al., 1996). Polarity inversion at the mastoid, therefore, may not be a critical feature for identifying the MMN in REM sleep.

During NREM sleep (restricted mainly to stage 2) the MMN was not apparent in either the 6 or the 1 semitone condition. Many previous studies have also failed to observe an MMN in NREM sleep (Loewy et al., 2000; Nashida et al., 2000; Nielsen-Bohlman et al., 1991; Nittono et al., 2001; Paavilainen et al., 1987; Sallinen et al., 1997; Winter et al., 1995). Those studies that have demonstrated an MMN in NREM sleep did so using a large extent of deviance (Ruby et al., 2008; Sabri & Campbell, 2005; Sabri et al., 2000, 2003; Sallinen et al., 1994). It is possible that this negativity represents the initial onset of a later, but much larger amplitude (often > 25 μV), N350. In the present study, there was no evidence of the N350 in the 6 semitone condition and the MMN was not apparent.

A significant MMN was also not apparent in the 1 semitone condition during REM sleep. A smaller number of trials were presented in the 1 than the 6 semitone condition. It is thus possible that considerably more trials would need to be presented to allow the extraction of this small amplitude response from the background EEG. Nevertheless, this pattern of results is reminiscent of those of Muller-Gass et al. (2006), who demonstrated an effect of attention on the MMN in the waking state, but only if the extent of deviance was small. Attention and consciousness do not appear to benefit the MMN elicited by highly perceptible deviants.

During definitive REM sleep, a P3a was not elicited. Some studies have indicated that a large, obtrusive deviant stimulus representing an increase in the intensity of the standard can elicit a P3a-like waveform during REM sleep (Cote & Campbell, 1999; Cote et al., 2001; Macdonald et al., 2008). A large decrease in intensity of the standard will not, however, elicit a P3a in REM sleep, even though it does so in the waking state (Macdonald et al., 2008). This suggests that a P3a can only be elicited during REM sleep following sufficient activation of the auditory transient detector system, the passive route associated with the N1 component. Even large activation of the change detector system, as indexed by the MMN, will not result in the interruption of the central executive in REM sleep. A P3a was also not elicited during NREM sleep, presumably because the change detection system was inactive, as reflected by the absence of an MMN.

The Näätänen (1990) model described the MMN as the outcome of a neural mismatch between the memory representation of previous standard stimuli and an incoming deviant stimulus. Recently, the mechanism underlying the MMN has been conceived as a process by which incoming stimuli are compared to a prediction, based on regularities extracted from previous stimulation (Winkler, 2007). This predictive mechanism explains MMN generation both in oddball paradigms, and in complex paradigms with no physically identical standard stimuli. To be consistent with the original Näätänen model, the newer predictive model also requires that the MMN to more abstract regularity violations be elicited regardless of the extent of attention allocated to the auditory channel, i.e., to operate at a pre-conscious level.

The detection of deviance in a two tone alternating pattern, such as that used in the present study, requires the extraction of several regularities from the auditory sequence (Horváth et al., 2001). The MMN to violations of an alternating pattern is present, although attenuated, when elicited by stimuli in the unattended channel of a dichotic listening task (Alain & Woods, 1997), and is unaffected by the attentional demands of difficult visual tasks in the waking state (Dyson et al., 2005; Sculthorpe et al., 2008). This might, however, be explained by the fact that subjects could sample the auditory channel even during these very difficult visual tasks (Muller-Gass et al., 2006). The present results indicate that the regularity-based MMN can be elicited during REM sleep, at least when tonal separation is large. This provides considerable support to the claim that regularity-based prediction and comparison with incoming stimuli can occur at a pre-conscious level of processing, supporting the emerging predictive model of the change detection system.

4. Method

4.1 *Subjects*

Ten young adults (7 male, 3 female, aged 20-30, mean = 24.1 years) volunteered to participate in the study. They spent a single night in the sleep laboratory. All reported normal hearing. None reported a history of hearing, neurological or psychiatric disorder. Subjects were asked to abstain from caffeine and alcohol use for 24 h prior to the study. Written informed consent was obtained prior to the study, and subjects received monetary honorarium as compensation. This study was carried out according to the Canadian Tri-

Counsel guidelines (Medical, Natural, and Social Sciences) on ethical conduct for research involving humans. Subjects arrived at the laboratory at approximately 20:00 in order to allow time for electrode application procedures and waking data collection.

4.2 *Data Acquisition*

The electroencephalogram (EEG) and electrooculogram (EOG) were recorded using tin electrodes. They were filled with electrolytic paste, and affixed to the scalp by gauze and to the skin by surgical tape. A limited scalp montage was employed to minimize disturbances to sleep. The EEG was therefore recorded from three scalp locations placed at midline frontal (Fz), central (Cz) and parietal (Pz) sites[4]. An active electrode was also placed on the left mastoid (M1). The nose was used as reference for all sites. A vertical EOG was recorded from electrodes placed on the supra- and infra-orbital ridges of the left eye. A horizontal EOG was recorded with an electrode placed at the outer canthus of the right eye, referenced to M1. Blinks, vertical eye movements and saccadic eye movements (associated with reading, while the subject was awake) could easily be distinguished from the random slow horizontal eye movements that typically appear in Stage 1 sleep. A ground electrode was placed on the forehead. Impedance at all electrode sites was reduced to below 5 kΩ.

The EEG and EOG signals were amplified with a time constant of 2 s and a 35 Hz low-pass filter. The signals were digitized at a 256 Hz sampling rate and stored continuously to hard disk.

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[4] EEG activity from the Pz scalp electrode was unavailable for some subjects, probably because of movement during the sleep period. The MMN is, however, very small at this recording site. Data analyses were therefore based only on the frontal and central recordings, channels where the MMN is maximum in amplitude.

4.3 *Procedure and Stimuli*

Following the placement of electrodes, subjects were taken to a separate double-walled, sound-attenuated testing chamber. Stimuli were presented to the left ear using EAR 3A insert earphones. This assured constancy of stimulus input in spite of movement during the all-night sleep period. The auditory pattern consisted of two alternating 70 dB SPL pure tones (A and B), each having a duration of 100 ms and a rise/fall time of 10 ms. Most MMN studies during sleep employ a rate of presentation of about 2 Hz. Therefore, the onset-to-onset interstimulus interval (ISI) was held constant at 500 ms. The frequencies of these tones varied in two different conditions. In the 6 semitone separation condition, the A and B frequencies were 841 and 1189 Hz, while in the 1 semitone separation condition, they were 1000 and 1059 Hz, respectively. Similar stimuli were employed by Alain et al. (1994). Deviants within this alternating standard pattern were a repetition of either the A or the B tone. Deviant repetitions had a probability of 0.067, and occurred at random under the constraint that the time between deviant presentations varied between 4 and 10 s. The auditory pattern was presented in blocks consisting of 600 stimuli. The duration of a block was therefore 5 mins.

In the waking state, subjects were asked to read a book of their choice and thus ignore the auditory stimuli. Horizontal eye movements were monitored to assure compliance with these instructions. Four blocks of each condition were collected in the waking condition, with a short break given between blocks. The waking data were collected from 22:00-23:30, then subjects were permitted to sleep. Auditory stimulus presentation commenced again at least 10 minutes after the onset of definitive stage 2 sleep (marked by delta activity in the EEG, spindles and K-Complexes). Two experienced raters scored the ongoing EEG as stages 2, 3, 4 or REM sleep using standardized Rechtschaffen and Kales procedures (1968). During sleep, blocks of auditory stimuli were presented in stages 2, 3 and REM. Because stage 3 occupies only a small portion of total sleep time, presentation of stimuli during NREM sleep mainly occurred in stage 2. Stimuli were not presented during stage 4 sleep. The small amplitude MMN is especially difficult to extract from the high amplitude delta activity associated with stage 4 sleep (Sabri et al., 2002). It was expected that if the MMN could be elicited in sleep, it would be when the MMN was relatively large in the waking state (i.e. during the 6 semitone condition). Presentation of the 6 semitone condition blocks of trials was therefore given priority. A minimum of 4 auditory blocks was presented for all subjects in both NREM and REM sleep. The 1 semitone condition was also presented, if time permitted. A minimum of 3 blocks was presented in NREM and REM for all subjects.

4.4 *Data Analysis*

4.4.1 *Sleep staging*

Off-line, the continuous EEG was again independently rated by 2 experienced scorers as being either NREM or REM sleep, using a 16 s epoch. The ratings rarely differed (fewer than 1% of epochs). When they did differ, the 2 raters attempted to come to a consensus. When no consensus could be reached, the epoch was excluded from further analyses. Stage changes (NREM to REM or REM to NREM) were exceedingly rare within the 5 min block of stimulus presentation. Brief periods of arousal or awakening were identified by the 2 raters and rejected from further analyses. Data analyses were therefore restricted to unambiguous stages NREM and REM sleep. In many cases, time permitted the presentation of more than 4 blocks of trials for the 6 semitone condition, especially within NREM sleep. In order to equate the number of trials averaged in the waking and sleeping states, the analysis was restricted to only 4 blocks of data, selected at random.

4.4.2 *ERP Averaging*

Eye movement and blink artifact were corrected using an algorithm operating in the time and frequency domains (Woestenburg et al., 1983). The continuous EEG was subsequently reconstructed into discrete 500 ms trials (or "sweeps") including a 100 ms pre-stimulus baseline. Any trials containing EEG activity exceeding ±100 μV were rejected from averaging. Single trials were sorted and averaged on the basis of stimulus type (standard or deviant), semitone condition (1 or 6 semitone separation), and state (waking, NREM, or REM). The resulting averages were digitally filtered using an inverted FFT algorithm with a bandwidth of 1.0-12.0 Hz (3 dB roll-off). All deviants, regardless of whether they were repetitions of the low or the high tone, were averaged together, as were all standards. The first 4 standard stimuli of each block, and the 4 standards following each deviant, were excluded from averaging. The mean number of non-rejected deviant stimulus trials available for averaging in the 6 semitone condition was 151 (*SD* = 8) in NREM, and 156 (*SD* = 10) in REM sleep. In the 1 semitone condition, the mean number of deviant stimulus trials accepted for averaging was 140 (*SD* = 12) in NREM, and 134 (*SD* = 33) in REM sleep.

4.4.3 *Statistical Analysis*

The MMN is best observed as a difference wave. The difference wave was computed by subtracting point-by-point the auditory standard from the deviant ERPs at each electrode site. The subtraction routine removes processing that is common to both the standard and the deviant, leaving only the difference in processing. The amplitudes of ERP components are often measured as a maximum single peak amplitude within a given latency range. Under conditions in which components are near baseline, the maximum peak amplitude scoring method can falsely quantify noise as an ERP component. To overcome this problem, Alho et al. (1989) employed a mean interval averaging procedure. Since a number of studies have indicated that the MMN is near or at baseline during NREM sleep, the data point averaging procedure was used in this study. The 400 ms post-stimulus sweep was divided into 8 intervals of 50 ms, beginning at stimulus onset. In each of these intervals, a mean amplitude was computed by averaging all data points within the window. The 100 ms pre-stimulus interval served as a baseline from which all amplitudes were measured.

Confidence intervals were computed at Fz, where the MMN is maximal, in each of the 8 latency intervals to determine whether the mean in each interval was significantly less than 0 μV ($p < .05$). This procedure is equivalent to computing a one-tailed *t*-test between the deviant and standard waveforms (Winer, 1971). To reduce the likelihood of chance significance, negativities were only considered to reflect an MMN if they occurred in the expected latency (100-250 ms), and inverted in polarity at M1. A problem with the mean interval averaging procedure is that the true amplitude might be "smeared" across or within the 50 ms intervals. Thus, if the existence of a significant MMN was confirmed in any condition, the MMN was also quantified as the average amplitude in the ±20 ms window surrounding the visually-identified peak in the grand average.

Figure Caption

Figure 1: Grand average ERP deflections in the 6 semitone condition across all waking and sleeping (NREM, REM) states. The "raw" standard and deviant ERPs are superimposed in the upper portion, while deviant-standard difference waves appear in the lower portion. Note the presence of an MMN (downward arrow) that inverts at M1 (upward arrow) in both the waking state. The MMN in the waking state occurred at about 185 ms. During REM sleep, a significant negativity was apparent at about 210 ms. However, only a small positive-going inversion was apparent at the mastoid. In NREM, no MMN is visible.

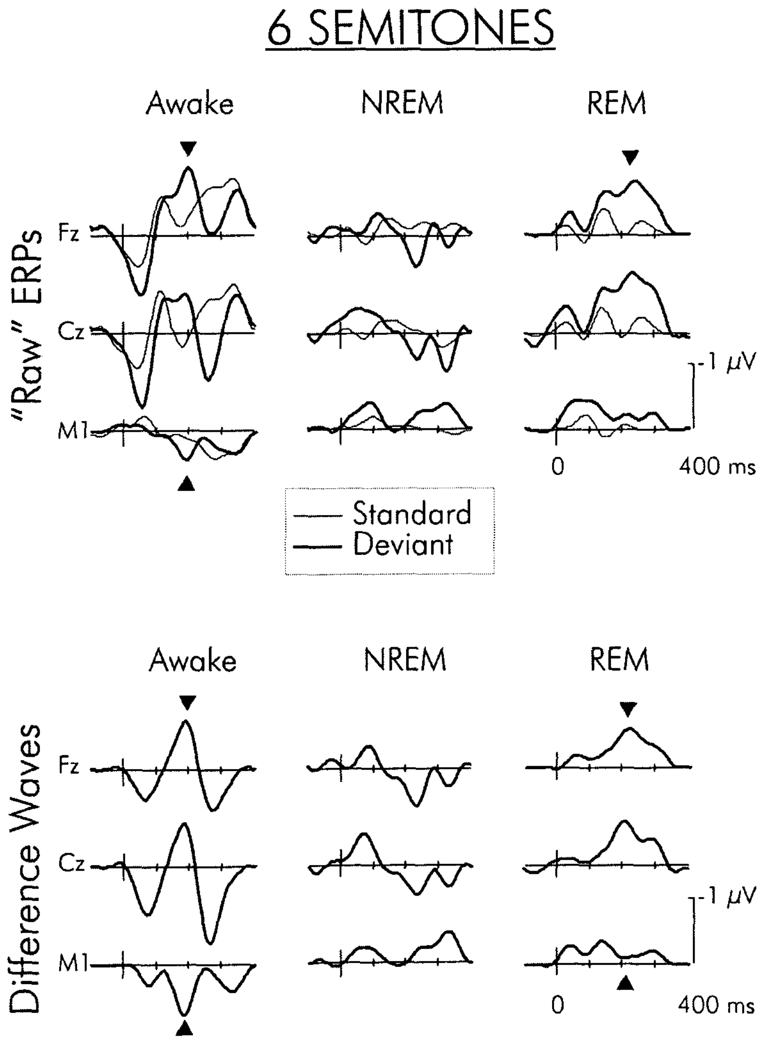

Figure Caption

Figure 2: Grand average ERP deflections in the 1 semitone condition across waking and sleeping states. "Raw" standard and deviant ERPs are again superimposed in the upper portion, while deviant-standard difference waves appear in the lower portion. In the waking condition (left column), a small, complex MMN is present that does not invert until about 200 ms. The amplitude of this MMN was not significantly different from the baseline level. No MMN was apparent in either NREM or REM sleep.

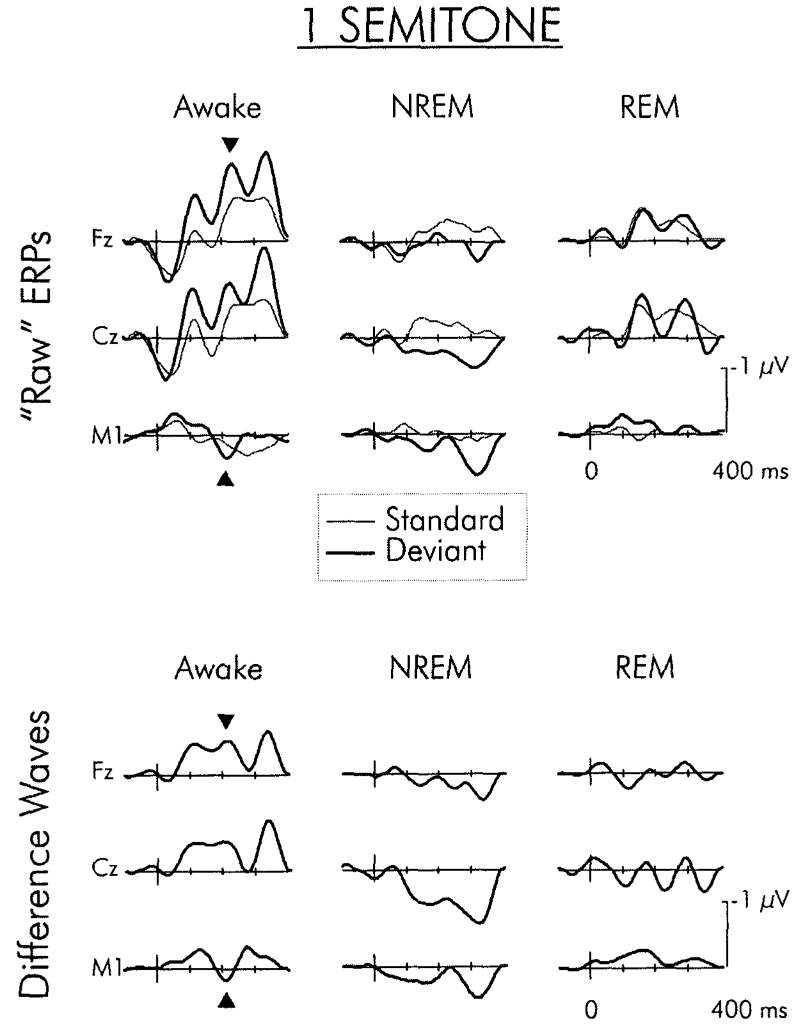

Table 1: Means and standard errors of the means (in parentheses) for amplitudes at Fz in each 50 ms interval of the 400 ms sweep.

	0-50	50-100	100-150	150-200	200-250	250-300	300-350	350-400
6 semitones								
Waking	0.24	0.49[b]	-0.06	-0.70[a]	-0.10	0.66[b]	0.29	-0.05
	(0.25)	*(0.26)*	*(0.22)*	*(0.28)*	*(0.30)*	*(0.34)*	*(0.46)*	*(0.20)*
NREM	-0.00	-0.28	-0.06	0.24	0.60	0.23	0.28	0.10
	(0.21)	*(0.37)*	*(0.57)*	*(0.69)*	*(0.67)*	*(0.73)*	*(0.66)*	*(0.29)*
REM	-0.10	-0.19	-0.22	-0.48[a]	-0.64[a]	-0.42	-0.19	-0.02
	(0.25)	*(0.19)*	*(0.21)*	*(0.20)*	*(0.27)*	*(0.34)*	*(0.38)*	*(0.15)*
1 semitone								
Waking	0.09	-0.27	-0.51[a]	-0.48	-0.52	-0.18	-0.62[a]	-0.38[a]
	(0.21)	*(0.23)*	*(0.23)*	*(0.37)*	*(0.30)*	*(0.26)*	*(0.24)*	*(0.13)*
NREM	0.00	-0.05	0.17	0.12	0.20	0.25	0.42	0.15
	(0.31)	*(0.34)*	*(0.46)*	*(0.51)*	*(0.40)*	*(0.42)*	*(0.61)*	*(0.37)*
REM	-0.15	0.04	0.22	-0.02	0.05	-0.13	-0.00	0.11
	(0.17)	*(0.14)*	*(0.24)*	*(0.25)*	*(0.25)*	*(0.23)*	*(0.25)*	*(0.09)*

For all conditions $n = 10$.

[a] Negative amplitudes that were significantly different from baseline (one-tailed $p < 0.05$).

[b] Positive amplitudes that were significantly different from baseline (one-tailed $p < 0.05$).

Chapter 4:

MMN to pattern violations does not vary with deviant probability.

1. Introduction

The mismatch negativity (MMN) is an ERP that signals the detection of change in the auditory modality. It consists of a negative enhancement in the ERP waveform to the regularity-violating deviant stimulus that peaks 100-250 ms from stimulus onset, and is best viewed in a difference wave computed by point-by-point subtraction of the standard from the deviant waveform. When a nose reference is used, the MMN demonstrates a frontocentral distribution and inverts at sites below the Sylvian fissure. This scalp distribution has been attributed to vertically-oriented, bilateral sources on the supratemporal plane, as well as a possible frontal source (Giard, Perrin, Pernier, & Bouchet, 1990).

Näätänen and colleagues first identified the MMN in 1978, using the oddball paradigm. In the oddball paradigm, a homogeneous sequence of identical standard stimuli is interrupted at rare and unpredictable times by a deviant stimulus with some changed feature. In this seminal study, as in much of the MMN research, the changed feature was tonal frequency. In the classic Näätänen model (Näätänen, 1990), the MMN was conceived as the outcome of a comparator process in which the features of an incoming stimulus are compared to those of a detailed neural representation of previous stimuli stored in sensory memory. This memory-trace comparison process may be best illustrated using the example of a frequency oddball paradigm. According to Näätänen, frequency-specific neurons begin in a state of homogeneous inhibition. Presentation of the standard stimulus then maintains inhibition in neurons corresponding to the tonal frequency of the standard, while neurons responding to other frequencies are released from inhibition.

Repetitions of the standard strengthen this stimulus-specific inhibition, and also increase excitability in the rest of the system. The more excitable the system is, the larger the MMN will be when a deviant stimulus is presented. The MMN, in this case, is considered to reflect the formation of a memory trace for the deviant stimulus.

Näätänen and Winkler (1999) describe the neural representation as a relatively long form of sensory memory called the stimulus representation. This stage of sensory memory follows the extraction of basic physical features and represents the stimulus as an integrated whole. More recent descriptions of the comparator process have departed from the classic memory-trace comparison hypothesis and describe the MMN as a comparison between the features of the incoming stimulus and either a model of the preceding auditory sequence, or a prediction based on that model (Schröger, 2007). Regardless of the exact nature of the comparison, the comparator mechanism underlying the MMN can still be described as a memory-based process.

There exists considerable evidence to suggest that the comparator mechanism underlying the MMN is strongly tied to auditory sensory memory. Measurement of the magnetic counterpart of the MMN, the mismatch field (MMF), under conditions of varied inter-stimulus intervals (ISIs), has demonstrated that the memory representation underlying the MMF lasts approximately 10 s (Sams, Hari, Rif, & Knuutila, 1993). This coincides fairly well with estimates of the duration of auditory sensory memory from behavioural measures (Watkins & Todres, 1980). Perhaps most importantly, the stimulus representation underlying MMN generation exhibits similar properties to other forms of memory. Studies using discrete trains of stimuli and varying the silent intervals between these trains demonstrate no MMN to deviant stimuli when they are presented at the first position of a train. This suggests that the memory underlying the MMN becomes dormant during the silent period. The stimulus representation can also be reactivated: deviants in the second position of the train, following one reminder presentation of the standard, once again elicit an MMN (Cowan, Winkler, Teder, & Näätänen, 1993; Winkler, et al., 2002). A single stimulus presentation is insufficient to establish a new representation of the standard (Sams, Hämäläinen, Antervo, Kaukoranta, Reinikainen, & Hari, 1985), thus an MMN to deviants in the second position must be based on a reactivated memory of the standard from the preceding train.

Although an MMN may be obtained even with very long ISIs, it becomes smaller and more variable at slower rates of presentation (Sabri & Campbell, 2001; Alain, Woods, & Ogawa, 1994; Sams, Hari, Rif, & Knuutila, 1993). The temporal interval between the deviant and the standard that immediately precedes it appears to be particularly important (Imada, Hari, Loveless, McEvoy, & Sams, 1993). Conversely, increasing the number of repetitions of the standard between successive deviants increases the amplitude of the MMN (Imada et al., 1993; Sams, Alho, & Näätänen, 1983).

This stimulus repetition effect presumably underlies the relationship between MMN amplitude and deviant stimulus probability. Numerous studies have demonstrated that the amplitude of the MMN varies inversely with deviant stimulus probability (Näätänen, Sams, Järvilehto, & Soininen, 1982; Sinkkonen, Kaski, Huotilainen, Ilmoniemi, Näätänen, & Kaila, 1996; Javitt, Grochowski, Shelley, & Ritter, 1998; Shelley, Silipo, & Javitt, 1999; Sato, et al., 2000; Sabri & Campbell, 2001; Sonnadara, Alain, & Trainor, 2006; Sato, et al., 2003). When deviant stimulus probability decreases, the number of standards presented between deviants increases, providing more reinforcement for the memory representation of the standard. With regards to stimulus-specific inhibition, and the classic memory-trace comparison hypothesis, the more often the standard is presented (i.e., the lower deviant probability is), the more excitable neurons corresponding to deviant features become, resulting in a larger MMN. Conversely, when deviant probability is high, a strong representation of the deviant stimulus can form in sensory memory. Thus, the comparator mechanism underlying the MMN may find more of a memory "match" than "mismatch", and the MMN may be diminished, or eliminated altogether. Both of these mechanisms are thought to contribute to reducing the amplitude of the MMN with increasing deviant probability.

The diminution of the MMN at longer ISIs and when fewer standards are presented between successive deviants has long been interpreted as a result of the rapid fading of sensory memory for the standard, providing further evidence that the amplitude of the MMN varies with the strength of its representation. Although this interpretation is parsimonious with the idea that the MMN reflects the outcome of a memory-based comparison process, there exist other compelling explanations for these effects. Manipulations of ISI may place the deviant stimulus out of context (i.e., temporally isolating it so that there is no contextually relevant standard against which to determine "deviance"), rather than demonstrating an effect of memory degradation (Cowan et al., 1993). Likewise, the relationship between the number of standards presented between deviants and MMN amplitude may not reflect effects on sensory memory. Using an abstract rule paradigm, in which the standard sequence consisted of tones that consistently either ascended or descended in frequency, Bendixen and Schröger (2008) found that increasing the number of standards presented before deviants did not affect the amplitude of the MMN. These results were interpreted as support for the all-or-none hypothesis of the MMN, which suggests that the amplitude of the MMN in the averaged waveform is only modulated by deviant discriminability (see Horváth, Czigler, Jacobsen, Maess, Schröger, & Winkler, 2008; Winkler, 2007 for a more detailed description of this concept).

It remains possible, however, that the MMN to abstract rules is less intimately tied to stimulus representations than other MMNs. Much of the MMN literature is based on "concrete rule" paradigms, in which rules are established by repeatedly-presented standard stimuli. The oddball paradigm represents one very simple kind of concrete rule: in the standard sequence, a single type of standard stimulus is presented repeatedly. Use of a concrete rule paradigm may allow both rules and exemplars of the standard sequence to be represented in sensory memory. Abstract rule paradigms, however, contain no standard physical stimulus that can be repeated: the standard rule must be extracted based only upon the relationships between successive, physically different tones. Rather than being based in part on exemplars, deviance detection in an abstract paradigm must be determined based solely on the rules that govern the standard sequence. Research using concrete rules has consistently demonstrated increases in MMN amplitude when more standards are presented between successive deviants (e.g., Imada et al., 1993; Sato, et al., 2000; Sabri & Campbell, 2001; Baldeweg, Klugman, Gruzelier, & Hirsch, 2004).

The popular oddball paradigm is one kind of concrete rule paradigm. Studies that have demonstrated an effect of deviant probability on the MMN have generally used oddball paradigms with tonal frequency deviants. However, such paradigms have long been criticized for not eliciting a "true" MMN. Since the auditory system is tonotopically organized, the frequencies of the standard and deviant tones in an oddball paradigm are handled by different afferent neuronal populations.With repeated presentations of the standard, a large proportion of the afferent neurons responding to the standard frequency will enter a refractory state, and the responsiveness of the population will diminish. The deviant stimulus, however, is presented much less often than the standard. Thus, a greater he afferent neurons in the population responding to the deviant frequency will tend to remain “fresh”, and produce a large response when stimulated. Any ERP component that varies with the state of refractoriness of afferent neuronal populations, therefore, will be larger to the deviant than the standard, and this difference will be retained in the classic deviant minus standard difference wave. One such ERP component is N1 (Näätänen & Picton, 1987). Thus, the deviant minus standard difference wave in a frequency oddball paradigm contains both the “true” MMN, and the difference in N1 activation between the standard and deviant tones (Jacobsen & Schröger, 2001). Since the MMN and N1 occur at similar latencies, with similar scalp distributions, disentangling the relative contributions of these ERP components to the observed deviance-related negativity (DRN) is often not possible.

N1 enhancement occurs in oddball paradigms because the standard is presented far more often than the deviant. Experiments that manipulate deviant probability change this ratio: as deviant probability increases, the disparity in how often the standard and the deviant are presented diminishes. Consequently, probability studies using oddball paradigms with frequency deviants cannot avoid influencing the amount of N1 enhancement contributing to the difference wave. At low deviant probability, N1 enhancement would contribute more to the DRN, while at high deviant probability, the contribution of N1 enhancement to the DRN would be diminished. This pattern of N1 enhancement exactly matches the reported effect of deviant probability on MMN amplitude.

The first study to examine the effect of deviant stimulus probability on the MMN was that of Näätänen, Sams, Järvilehto, and Soininen in 1982. Deviant stimulus p was 0.02, 0.10, or 0.50 in different conditions, and an extremely small frequency separation was used (44 Hz). The advantage of using such a small frequency separation is that the standard and deviant frequencies largely activate the same neuronal populations, and as such, the deviant should not activate "fresh" afferents. No MMN was obtained in the $p = 0.50$ condition, and no effects of probability were obtained between the $p = 0.10$ and the $p = 0.02$ conditions when the group was analyzed as a whole. Separate statistical tests within each subject revealed a significant effect of probability in 2 of the 6 subjects.

Later studies demonstrated much more robust effects of deviant probability on MMN amplitude, but used oddball paradigms with rapid rates of presentation, and moderate to large tonal frequency deviants (Sinkkonen et al., 1996; Shelley et al., 1999; Sato, et al., 2000; Sabri & Campbell, 2001; Sato, et al., 2003). Such rapid rates of presentation and large frequency separations increase the risk of N1 enhancement contributing to the DRN. In addition, one study demonstrated an effect of deviant probability on the amplitude of the MMN to location deviants (Sonnadara et al., 2006), but oddball paradigms with location deviants are also subject to N1 enhancement (Schröger & Wolff, 1996).

One way to avoid fresh afferent activation and N1 enhancement is to use a non-oddball paradigm in which the deviant is not created by changing a physical feature of the standard. The MMN can be elicited by violations of any type of regularity, of which a physical change in an oddball paradigm is only one example. The oddball paradigm represents what Picton, Alain, Otten, Ritter, and Achim (2000) call simple invariance: all of the standard stimuli are identical, and deviants possess some changed feature. It is the homogeneity of the standard stimuli in simple invariance that invites N1 overlap. Violations of what Picton and colleagues call complex, hypercomplex, pattern, and abstract types of invariance also elicit the MMN, and in many cases, these paradigms do not involve a physically identical, homogeneous standard stimulus. N1 enhancement, therefore, is less likely to occur in these paradigms.

The current experiments use what Picton and colleagues call pattern invariance to investigate the effect of deviant probability on the MMN. Specifically, it uses a pattern of two alternating pure tones. The MMN to violations of a two-tone alternating pattern was first demonstrated by Nordby and colleagues in 1988(b). In this pattern, two tones of different tonal frequency (A and B) consistently alternate in the standard sequence (ABABABAB). MMN-eliciting violations are repetitions of either the A or the B tone (e.g., ABABABBAB). Since a deviant stimulus in this paradigm is physically identical to the standard stimulus that precedes it, the N1 response to deviant stimuli should, if anything, be diminished (Butler, 1968). Thus, a "true" MMN should be elicited without any overlapping N1 enhancement. Furthermore, this two-tone alternating pattern can be classified as a concrete rule paradigm, which could be represented in sensory memory by both representations of rules and rule exemplars (e.g., an A-B pair, or a B-A pair).

In keeping with the Näätänen model, deviants in such a pattern elicit an MMN that is relatively automatic. It is elicited when subjects are engaged in a difficult continuous visual object tracking task (Sculthorpe, Collin, & Campbell, 2008), and even during stage REM of sleep (Sculthorpe, Ouellet, & Campbell, 2009). An effect of deviant probability on MMN amplitude in a pattern paradigm would constitute powerful evidence in favour of a genuine relationship between probability and the MMN, and would support the idea that the MMN varies with the strength of the representation of the standard. Experiment 1 investigates the effect of deviant probability using both a pattern and, for the purpose of comparison, a classic oddball paradigm.

2. Experiment 1

2.1 Methods

2.1.1 Subjects

Twelve young adults (6 female, aged 20-30, mean = 25.2 years), all with no history of neurological or hearing problems, volunteered to participate in the study. Written informed consent was obtained prior to the study, and participants received monetary honorarium as compensation. The study was carried out according to the Canadian Tri-Counsel guidelines (Health, Natural, and Social Sciences) on ethical conduct for research involving humans.

2.1.2 Stimuli and Procedure

The acoustic stimuli consisted of two tones (A and B) that, in different conditions, were presented in either an alternating pattern (ABABAB...) or an oddball sequence. The stimuli were presented binaurally through EAR 3A insert earphones. All tones had an intensity of 70 dB SPL, a duration of 100 ms, and a rise/fall time of 10 ms. Both conditions employed a constant onset-to-onset ISI of 500 ms. The tonal frequencies of A and B were 841 and 1189 Hz, respectively, representing a 6 semitone separation between the two tones. Randomly-occurring deviants in the alternating standard pattern were a repetition of either the A or the B tone, e.g., ABABBAB. In a separate condition, an oddball paradigm was run in which the 841 Hz stimulus (A) served as the frequently occurring standard while the 1189 Hz stimulus (B) served as the randomly presented deviant, e.g., AAAABAA. The deviant tones were presented at a high (p = 0.16) or rare (p = 0.02) probability, in separate conditions. Thus there were 4 experimental conditions, representing all combinations of the 2 levels of probability (high vs. rare), and 2 types of sequences (oddball vs. pattern). In order to collect enough deviants to observe the averaged MMN, 4 blocks of stimuli were presented under each of the rare deviant probability conditions, while 2 blocks were presented under high deviant probability conditions. Thus, 12 blocks were administered to each subject, in randomized order. A short break was provided after every block. During EEG recording, subjects were seated in a dimly lit, acoustically buffered room, and watched a self-selected movie presented silently with subtitles under instructions to ignore all auditory stimuli.

Using an alternating pattern places an upper limit of 0.16 on deviant stimulus probability. This is because the fundamental unit of the standard alternating pattern is a stimulus pair (A-B). Therefore the probability of deviance is twice as high as the sequential probability suggests. For instance, at high deviant probability, when deviant p is 0.16, 32% (nearly 1/3) of the pairs in the sequence contain a deviant repetition. Since at least two examples of the standard pair are necessary between deviants to establish what is "standard" in the sequence, a maximum of 1/3 of the pairs in the sequence can contain a deviant repetition.

2.1.3 Data Acquisition and Analysis

The EEG was recorded from 10 scalp sites of the 10–20 system, including Fz, F3, F4, Cz, Pz, C3, C4, T7, T8, and Oz, using tin electrodes mounted in an elasticized cap (ElectroCap International Inc., Eaton, OH). Two additional tin electrodes were placed at the left and right mastoids (M1, M2). The nose was used as reference for all sites. A vertical EOG was recorded from the supra- and infra-orbital ridges of the left eye, and a horizontal EOG was also recorded with electrodes placed at the outer canthus of each eye. Impedance at all electrode sites was reduced to below 5 kΩ.

The EEG and EOG signals were sampled at a rate of 256 Hz, with a 2 s time constant and a high filter set to 35 Hz, and stored for offline analyses. Eye movement and blink artifact were corrected using an algorithm operating in the time and frequency domains (Woestenburg, Verbaten, & Slangen, 1983). The continuous EEG was baseline corrected and then subsequently reconstructed into discrete 500 ms epochs including a 100 ms prestimulus baseline. Any trials containing EEG changes exceeding ±100 μV were rejected from averaging. The single trials were sorted and averaged on the basis of sequence type (oddball or pattern), stimulus type (standard or deviant), and probability condition (high or rare deviant probability). The resulting averages were digitally filtered using an inverted FFT (windowing) algorithm with a low-pass filter of 20 Hz, and a high-pass filter of 0.8 Hz. Data in the last 50 ms of the epoch are distorted by this procedure. All deviants in the alternating pattern condition, regardless of whether they were low or high tones (repetitions of A or B), were averaged together, as were all standards. In the alternating pattern condition, the first 4 standard stimuli (2 standard pairs) of each auditory run, as well as the 4 standards following each deviant were excluded from averaging. In the oddball condition, the first 2 standard stimuli of each run, and the 2 standards following each deviant were omitted.

The 100 ms pre-stimulus interval served as a baseline from which the ERPs were scored. The amplitude of the MMN was measured in the difference wave computed by subtracting point-by-point the auditory standard from the deviant ERPs at each electrode site. MMN amplitude was computed as the average of all data points in the 20 ms period surrounding peak deflection identified in the grand average.

2.2 Results

Figure 1 depicts the deviant minus standard difference waves for both oddball and patterned stimuli under high and rare deviant probabilities. The MMNs, peaking at about 190 ms, exhibited a fronto-central maximum and inverted in polarity at the mastoids. Planned contrasts were used to examine effects of probability within each sequence type (oddball and pattern) at Fz and M1. Since effects were expected to occur only in one direction (many previous studies have indicated that the MMN is smaller in high probability conditions), an alpha level of 0.10 was used to determine significance. Planned contrasts at Fz revealed a significant effect of probability in the pattern condition, $p < 0.05$, and a non-significant trend towards an effect of probability in the oddball condition, $p = 0.11$. These results are consistent with the established literature, with the amplitude of the MMN diminishing with increased deviant probability. Some research suggests that there may be differential effects of probability on the frontal and temporal sources of the MMN (Sato, et al., 2000; Sato, et al., 2003). The MMN recorded at the mastoid is often used as a measure of the extent of activation of the temporal source. Planned contrasts were also carried out at M1 which revealed a significant effect of probability in both the oddball, $p < 0.01$, and the pattern condition, $p < 0.10$. Again, the amplitude of the MMN decreased with increasing deviant probability. The mean amplitudes of MMN at Fz and M1 are summarized in Table 1 for all conditions.

2.3 Discussion of Experiment 1

Experiment 1 indicates that the MMN elicited to deviants in the oddball sequence is larger than that to pattern violations. Since the MMN observed in the oddball condition is probably a DRN composed of a summation of an MMN and an N1, it is not surprising that its amplitude is larger than the "true" MMN elicited by pattern violations.

Overall, the results of Experiment 1 appear to support previous findings of MMN amplitude variation with deviant stimulus probability. The effect of deviant stimulus probability on MMN amplitude was somewhat more robust in the pattern than in the oddball condition. This was not entirely unexpected, given that $p = 0.16$ is not a particularly high level of deviant probability in an oddball paradigm. Surprising, however, is the fact that the effect of deviant probability was significant at the mastoid, but only approached significance at Fz. These results are contrary to the findings of Sato and colleagues (2000, 2003), who found deviant probability to affect frontal, but not temporal sources of the MMN. These differences may derive from the different amount of N1 enhancement elicited by the present paradigm and by that of Sato and colleagues, who used a much larger extent of deviance (standards were 1000 Hz, deviants were 2000 Hz).

Deviants in the pattern condition were created by a repetition of the previous stimulus, and therefore the elicitation of the MMN cannot easily be explained by differential refractoriness in afferent neuronal populations. As such, the effects of deviant probability should not be mediated by N1 enhancement. The amplitude of the MMN elicited using this pattern varied with deviant probability at both Fz and M1. The fact that the MMN varied between high and rare probability conditions would appear to provide strong evidence of a genuine effect of deviant probability on MMN amplitude. Nevertheless, there exists an alternate explanation for the apparent effect of deviant probability under pattern conditions.

Deviance detection in a pattern is not well explained by the classic memory-trace comparison process described in Näätänen's model (1990). While standard exemplars (e.g., A-B or B-A pairs) may be maintained in sensory memory, the memory representation of the pattern also includes rules, or regularities. Horváth and colleagues (2001) demonstrated that a two-tone alternating pattern, such as that used in the present study, is represented in sensory memory by two levels of rules: local rules describing the relationships between adjacent tones (e.g., B follows A, A follows B), and global rules describing general regularities in the overall sequence (e.g., every second tone is B). In the type of sequence used in the pattern condition of Experiment 1, repetition deviants are immediately followed by an alternation (e.g., ABABABB̲*A*B). This immediate return to alternation means that local rules (e.g., A always follows B, B always follows A) are consistent throughout the sequence, but the global rules (e.g., every second tone is B) change following each deviant. If every second tone was B preceding the deviant, then following the deviant, every second tone will be A. The subjective experience of this instability in the global rules of the alternating sequence is a loss of rhythm. In the high deviant probability pattern condition, the global rules change quite often, on average after every 6 stimuli, or every 3 s. It is conceivable that the lack of consistent higher-level global rules under these conditions results in a poorer representation of the pattern in sensory memory, making it more difficult to perceive violations of the pattern. The amplitude of the MMN is also affected by the perceptibility of deviants, and is larger to deviants that are more accurately detected under active task conditions (Sams, Paavilainen, Alho, & Näätänen, 1985; Muller-Gass, Stelmack, & Campbell, 2006; Sculthorpe, Stelmack, & Campbell, 2009). It is possible, therefore, that the observed differences in MMN amplitude between the high and rare deviant conditions of the pattern condition reflect deviant perceptibility, rather than an effect of probability.

Experiment 2 tested this possibility by employing a slightly different alternating pattern in which deviants were followed by another repetition (i.e., ABABABB*B*AB), thus preserving the global rules of the sequence. To increase the resolution of the effects of deviant probability on the amplitude of the MMN, this pattern was presented at 4 levels of probability.

3. Experiment 2

3.1 Methods

3.1.1 Subjects

Eleven young adults (4 female, aged 18-27, mean = 21.7 years) volunteered to participate in the study, which was carried out using the same exclusion criteria and ethical guidelines as Experiment 1. One of these subjects participated in Experiment 1.

3.1.2 Stimuli and Procedure

The tones and procedures were the same as those used in Experiment 1, but the pattern was slightly different. Experiments 1 and 2 both use the same standard pattern, an alternation of tones A and B (i.e., ABABABAB). In the pattern used in Experiment 1 (called the "single deviant" pattern), deviant repetitions (e.g., ABABAABAB) were immediately followed by a return to alternation (e.g., ABABAA*B*AB). This immediate return to alternation caused the global rules of the sequence to change: if every second tone was B, then following a deviant, every second tone was A. In the pattern used in Experiment 2 (called the "double deviant" pattern), deviants are followed by another repetition (e.g., ABABAA*A*BAB). This second repetition preserves the global rules of the sequence: even after a deviant, global rules remain the same (e.g., every second tone is always B). See Figure 2 for an illustration of the differences between single and double deviant patterns. Deviants were presented at 4 levels of probability: high ($p = 0.16$), moderate ($p = 0.08$), low ($p = 0.04$), and rare ($p = 0.02$). Four blocks each were collected under the low and rare deviant probability conditions, while 2 blocks each were collected under the moderate and high deviant probability conditions. Therefore 12 blocks were administered to each subject, in randomized order. A short break was offered after every 2-3 blocks.

3.1.3 Data Acquisition and Analysis

Data acquisition and analyses were identical to that employed Experiment 1.

3.2 Results

The deviant minus standard difference waveforms for all conditions are illustrated in Figure 3. Again an MMN is apparent with a peak latency at approximately 200 ms in all conditions. Under all conditions, the MMN is maximal at fronto-central sites and inverts in polarity at the mastoid. Mean amplitudes for the MMN are again summarized in Table 1 for all conditions. One-way ANOVAs with repeated measures on deviant probability were run at Fz and M1 to test for the effect of deviant stimulus probability. Probability had no effect on the amplitude of the MMN at either Fz or M1 (in both cases, $F < 1$).

3.3 Discussion of Experiment 2

Probability had no significant effect on the amplitude of the MMN measured at either the frontal or the mastoid site when the double deviant pattern was used. The results of Experiment 1, in which a single deviant pattern was employed, did find an effect of deviant probability on MMN amplitude. This could, however, have been a result of also inadvertently altering perceptibility of the deviant pattern. Recall that two-tone alternating patterns are represented in sensory memory by at least 2 types of rules: local rules that describe the relationships between adjacent tones, and global rules that describe general regularities of the overall sequence. In the single deviant pattern, the immediate return to alternation after a deviant stimulus means that the global rules of the pattern change after every deviant (e.g., if every second tone was B, then after the deviant, every second tone is A). At high deviant probability, this occurs quite often, on average every 3 seconds. This may result in a poor representation of the standard sequence in sensory memory, making deviants difficult to detect. In Experiment 2, the use of a double deviant pattern supported the global rules of the sequence (e.g., if every second tone was B, then even after a deviant, every second tone continues to be B). Thus, even at high deviant probability, the local and global rules of the pattern are consistent, and deviant perceptibility should not be affected by probability. In this case, the manipulation of deviant probability no longer affected the amplitude of the MMN. Experiment 2, therefore, suggests that the effects of deviant probability that were obtained in Experiment 1 may be attributable to deviant perceptibility.

In Experiments 1 and 2, subjects were instructed to ignore the auditory sequence, thus effects on perceptibility of the deviant pattern could only be inferred on the basis of the MMN. Perceptibility is typically measured under active detection conditions, primarily on the basis of detection accuracy. More perceptible targets should be detected more accurately than less perceptible targets. Experiment 3 thus employed an active task in which subjects were instructed to detect the occurrence of a violation of the pattern. Both single and double deviant patterns were employed and again, deviant probability was manipulated. If increasing deviant probability decreases deviant perceptibility in the single deviant pattern, then it would be expected that accuracy will decrease as deviant probability increases. In the double deviant pattern, on the other hand, deviant perceptibility should be unaffected by probability, and as such, accuracy should not be affected by deviant probability.

4. Experiment 3

4.1 Methods

4.1.1 Subjects

Eleven young adults (8 female, aged 19-35, mean = 26.6 years) volunteered to participate in the study, which was carried out using the same exclusion criteria and ethical guidelines as Experiment 1. One of these subjects had participated in Experiment 1, and another had participated in Experiment 2.

4.1.2 Stimuli and Procedure

Experiment 3 was an active detection task using stimuli identical to the patterned auditory stimuli from Experiments 1 and 2 (single and double deviant, respectively). In separate conditions, the deviant tones were presented at a high (*p* = 0.16) or rare (*p* = 0.02) probability. Thus there were 4 experimental conditions, representing all combinations of the 2 levels of probability (high vs. rare), and 2 types of sequences (single vs. double deviant). Each block of 250 auditory stimuli had a duration of approximately 2 min. In order to collect approximately the same number of responses to deviants under the high and rare probability conditions, 6 blocks were collected under each of the rare deviant probability conditions, while 1 block was collected in high deviant probability conditions. Therefore 14 blocks were administered to each subject, in randomized order. A short break was offered after every 4-5 blocks.

In this active detection task, participants pressed a computer spacebar when they detected a deviant (a repetition of the preceding stimulus). They were instructed to respond as quickly and accurately as possible. To account for the second repetitions in the double deviant pattern, subjects were additionally instructed not to respond to repetitions that immediately followed a target, if they occurred. Each subject was given a 1 min practice with each type of stimulus condition (4 min total) to ensure they understood the task instructions. Responses were considered correct if they occurred within 250 - 2000 ms of deviant stimulus onset. No EEG was recorded.

4.2 Results

The behavioural results of Experiment 3 are summarized in Table 2. Planned comparisons were employed to examine the effect of probability (high vs. rare) within each pattern type (single vs. double deviant). Planned comparisons were also performed to examine the differences between the two pattern types at each level of probability. The behavioural measures provided four different measures of performance. A correctly detected deviant was classified as a hit and the proportion of hits as the hit rate (HR). The speed at which the deviant was detected was measured as the reaction time (RT). The mean of individual trial RTs was computed for each subject, as well as the standard deviation around the mean of these RTs (SDRT). A response to the standard was classified as a false alarm (FA) and the number of FAs was reported within each condition. There were, however, too few FAs to reliably permit the computation of the RT on the FA trials.

4.2.1 Hit Rate

The four planned contrasts were performed for each behavioural measure: high versus rare probability in the single deviant pattern, high versus rare probability in the double deviant pattern, single versus double deviant pattern under high deviant probability, and single versus double deviant pattern under rare deviant probability. In the case of HR, effects were expected to occur in a specific direction (HR was expected to be lower in the single deviant pattern, and under high deviant probability), thus the alpha level was set at 0.10.

Importantly, within the single deviant pattern, a significant effect of deviant probability was found, $p < 0.10$. As expected, HR was lower when they were presented at high (HR = 0.92) than rare (HR = 0.98) probability. In the double deviant condition, the accuracy of deviant detection was very similar in the high (HR = 0.97) and rare (HR = 0.99) probability conditions, thus there was no significant effect of deviant probability, $p > 0.20$. Consistent with these results, at high deviant probability, deviants were detected more accurately in the double than the single deviant pattern, $p < 0.10$. At rare deviant probability, there was no significant difference in the detection of deviants between the single and the double deviant patterns, $p > 0.20$.

4.2.2 False Alarms

Planned contrasts for FAs were run with an alpha level of 0.05 because no specific effects were predicted on the basis of the literature. Within both the single and the double deviant pattern, subjects made significantly more false detections in the rare than the high deviant probability conditions, $p < 0.05$ in both cases. Within high deviant probability, and within rare deviant probability, there were no significant differences in the number of false detections made in the single and the double deviant patterns, $p > 0.20$ in both cases. Thus, FAs varied only as a function of probability of deviant occurrence.

4.2.3 Reaction Time

As for FA, planned contrasts for mean RT were run with an alpha level of 0.05. Within the single deviant pattern, a significant effect of deviant probability was found, $p < 0.05$. Subjects responded significantly faster in the high probability condition (RT = 446 ms) than the rare probability condition (RT = 498 ms). In contrast, in the double deviant pattern, the speed at which subjects responded was similar in the rare (RT = 510 ms) and high (RT = 490 ms) probability conditions, $p > 0.20$. In the high deviant probability condition, subjects responded faster in the single deviant pattern (RT = 446 ms) than the double deviant pattern (RT = 490 ms), $p = 0.05$. At rare deviant probability, there was no significant difference in RT between the single and the double deviant patterns, $p > 0.20$.

4.2.4 Standard Deviation of Reaction Time

Planned contrasts for SDRT were performed with alpha set at 0.05. There was no significant effect of deviant probability either within the single deviant pattern, $p > 0.20$, or the double deviant pattern, $p > 0.10$. Within the high deviant probability condition, however, subjects response times were more variable in the double (SDRT = 136 ms) than the single deviant pattern (SDRT = 108 ms), $p < 0.05$. Within the rare deviant probability condition, there were no significant differences between the single and double deviant patterns, $p > 0.20$. This suggests that the SDRT was mainly increased in the high probability condition of the double deviant pattern.

4.3 Discussion of Experiment 3

In Experiment 3, the HR results indicate that in the single deviant pattern, deviant probability influences the accuracy with which subjects can detect pattern violations. Specifically, the HR for deviant detection was higher when they were presented relatively rarely, versus when they were presented more frequently. A higher HR may, however, be achieved by the adoption of a liberal response strategy. There were also more FAs when deviants were presented rarely.[1] Thus, when deviants were presented rarely, subjects may have adopted a more liberal response strategy, achieving an apparent high detection rate for the deviants by also erroneously responding to standards. In the double deviant pattern, the HR was not affected by deviant probability, yet FA was still higher when deviants were presented less frequently. Again, this might imply that the perception of the deviants in the rare probability condition was not as high as the HR implies. The high HR might have been accomplished by allowing for more false detections of the standard. These interpretations must, however, be made with caution. The number of FAs was very low in all conditions while, on the other hand, the number of correct detections for the deviants was very high.

The differences between the single and double deviant patterns are also revealed when the high deviant probability condition is considered alone. At high deviant probability, deviants were correctly detected more often in the double than the single deviant pattern. However, FA was not different between the two types of patterns at high deviant probability. Therefore, the

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[1] Ideally, in signal detection theory, perceptibility (or "discriminability") is measured by d', calculated by HR/FA rate. Unfortunately, d' can be much distorted when the false alarm rate is very low, as was the case in this experiment.

higher HR in the double deviant pattern cannot be attributed to a more liberal response strategy. It is possible, however, that the second deviant in the double deviant pattern provided a 'reminder' for subjects to respond. Nevertheless, on average, in the double deviant pattern at high probability, subjects responded before the presentation of the second deviant (490 ms). At rare deviant probability, accuracy did not significantly differ between the two types of patterns, and neither did the FA rate.

Other performance measures revealed that the behavioural effects of the probability manipulation were quite complex. Overall, subjects tended to respond faster when deviants were presented more frequently. Thus, in the high probability conditions, in which deviants occurred fairly frequently, subjects responded more quickly. Planned contrasts revealed that this effect was only significant in the single deviant pattern. Furthermore, when the high probability condition is considered alone, RT was faster in the single deviant pattern than the double deviant pattern. In studies of perception, perceptibility is often measured in part by RT, and longer RTs are generally considered to be a reflection of difficulty in making a perceptual discrimination. Thus, taken alone, the RT results might suggest that at high deviant probability, deviants are more perceptible in the single than the double deviant pattern. Accuracy, as measured by HR, however, suggests that deviants are more perceptible in the double than the single deviant pattern.

The reason for this contradiction may lie in the variability of the RTs (SDRT). At high deviant probability, RTs were more variable in the double than the single deviant pattern. It is difficult to determine what the cause of this increased variability might be. It should, however, be recalled that in the double deviant pattern, subjects were instructed not only to respond to the deviant repetition, but also to suppress their response to the second repetition. The increased cognitive load required by making this double decision at a rapid rate of target delivery may have resulted in a more variable speed of responding.

Studies that are designed to examine the relationship between deviant perceptibility and MMN amplitude have typically manipulated deviant perceptibility by varying the extent of deviance within an oddball paradigm, for instance, by increasing the frequency separation between standard and deviant tones (Sams, Paavilainen, et al., 1985; Muller-Gass et al., 2006). By contrast, the perceptibility effects examined in Experiment 3 were far more complex. Low deviant perceptibility conditions also entailed a more rapid rate of target delivery. As a consequence, performance demands changed between conditions. This atypical design may have produced effects that are difficult to interpret according to the classic perceptibility literature. Most problematic among these effects is the relationship between HR and RT. In perceptual studies, as HR increases, RT decreases. However, in the high probability conditions of Experiment 3, performance demands were changed by the more rapid delivery of targets. This rapid rate of delivery appears to have had its own influence on the strategies employed by the subjects to perform the task. Specifically, subjects speeded their responses when targets were delivered more quickly. Overall, this inverted the relationship between HR and RT. In addition, in the double deviant pattern, subjects had to execute a double decision regarding whether or not to respond. This increased cognitive load may have contributed to the increased variability in RT observed in the high probability condition of the double deviant pattern.

In general, however, the HR effects seem to indicate that deviants were least perceptible in the high deviant probability condition of the single deviant pattern. This interpretation is not without its difficulties: in the double deviant pattern, the second deviant may have provided a 'reminder' for subjects to respond. This problem would appear to be unavoidable at fast rates of presentation (e.g., the present 500 ms ISI). Slower rates of presentation, however, are not a viable solution. The presumed perceptibility effect in the single deviant pattern, at high probability, is dependent on rapid deviant delivery, and thus, frequent changes to the global rules of the pattern. Slowing the rate of delivery, even to an ISI of 1000 ms, would cause the global rules of the pattern to change every 6 seconds, rather than every 3 seconds, and the effect of probability on perceptibility may be lost. It is, therefore, difficult to conceive of a behavioural test that could examine the differences in perceptibility effects between Experiments 1 and 2 without the inherent complexity of the present experiment. Despite these problems, the perceptibility hypothesis offers the most plausible and parsimonious explanation for the different effects of probability on the MMN in the single and the double deviant patterns, and the behavioural data of Experiment 3 is roughly in line with the predictions of that hypothesis.

5. General Discussion

Three experiments were carried out to examine the effect of deviant probability on MMN amplitude. In Experiment 1, effects of probability on MMN amplitude were observed in both the oddball and the patterned sequence. While the demonstration of probability effects in the pattern condition of Experiment 1 could constitute strong evidence for a genuine effect of deviant probability on MMN amplitude, it remained possible that it was a confound of deviant perceptibility. Deviants might have been more readily perceived in the rare than the high probability condition in this single deviant pattern. Indeed, when subject were asked to overtly detect the deviants in the single deviant pattern (Experiment 3), accuracy of detection was higher when deviants occurred infrequently. When the standard (ABABAB) pattern is violated in the single deviant pattern (ABABBAB or ABABAAB), the local rules (B follows A, A follows B) continue to apply, but the global rules change (e.g., every second tone was B, but following a deviant, every second tone is now A). When deviant probability is high, the global rules of the sequence change on average every 3 s, and as such, only local rules may be available for constructing a memory representation of the standard alternating sequence. If an accurate representation of the standard pattern is not available, the pattern violations may be more difficult to detect (i.e., deviants may be less perceptible). Thus, when deviant probability is changed in the single deviant pattern, the loss of consistent global rules causes deviant perceptibility to change as well.

In Experiment 2, second repetitions were presented following deviant stimuli (ABABB*B*AB). In this double deviant pattern, neither local rules (B follows A, A follows B), nor global rules (e.g. every second tone is B) change following the occurrence of a deviant. Deviants were presented at 4 levels of probability to offer better resolution on any possible trend towards an effect of deviant probability, but there was no effect of deviant probability on MMN amplitude at either Fz or M1 ($F < 1$ in both cases). These results suggest that when deviant perceptibility is controlled, its probability of occurrence has no effect on MMN amplitude. This was confirmed when subjects were asked to actively detect deviants (Experiment 3). When the double deviant pattern was employed, the probability of deviant occurrence did not affect accuracy of its detection. By contrast, when the single deviant pattern was employed, probability of deviant occurrence did affect the accuracy of its detection. Thus, when global rules are preserved, the probability of deviant occurrence does not affect the perceptibility of pattern violations. Further, deviants presented at a high probability were significantly more difficult to detect in the single than the double deviant condition. This is in accordance with the perceptibility hypothesis.

These results thus suggest that deviant probability has little genuine effect on MMN amplitude when the possibility of fresh afferent activation and N1 enhancement is controlled through the use of a patterned sequence. Importantly, the relationship between deviant probability and MMN amplitude may only properly be observed when the auditory sequence that is used allows deviant probability to be manipulated without also influencing its perceptibility, as in the present double deviant pattern. The present results also do not support previous findings of a differential effect of deviant probability on the frontal and temporal generators of the MMN, in which the frontal generator of the MMN is triggered only by more salient, rare deviants (Sato, et al., 2000).

The suggestion that MMN amplitude does not vary with deviant probability is difficult to reconcile with the classic memory-trace explanation of the MMN. However, the results of a substantial number of studies have now accumulated that are poorly explained by the classic memory-trace comparison process. Since there is often no physically homogeneous standard stimulus in complex, hypercomplex, pattern, and abstract forms of invariance, as described by Picton and colleagues (2000), deviance detection in these paradigms cannot easily be explained by a process of stimulus-specific inhibition. More modern theories describe a pre-conscious mechanism that creates models of the auditory environment. Incoming stimuli are then compared either to the models themselves, or to the predictions made by those models (Schröger, 2007). Thus, in the oddball paradigm, the frequent repetition of the standard stimulus (AAAA) may be represented by a model that is defined by one local rule: A is followed by another A. The prediction made by this model is that the next stimulus encountered by the system should also be A. A deviant stimulus (B), elicits an MMN either because it violates the local rule (A is followed by A), or because it does not match the predicted input (A). In model- or prediction-based hypotheses of MMN generation, the MMN is thought to reflect updating of the model following the detection of a stimulus that differs from its predictions (Winkler, Karmos, & Näätänen, 1996; Winkler, 2007). The present results indicate that more frequent repetitions of the standard do not produce increased excitability of the MMN generating system, as would be predicted by the classic memory-trace comparison hypothesis. Thus, the present evidence is more consistent with model- or prediction-based hypotheses of MMN generation.

In all 3 experiments, an upper limit of 0.16 was placed on deviant probability, to ensure that at least 2 presentations of the standard pair (A-B) would occur between successive deviants. As such, even at the highest deviant probability, the sequence always contained a "standard". The present results, therefore, may indicate that as long as there is a standard in the sequence, increasing the number of repetitions of that standard, and presumably strengthening the memory representations of the standard sequence, does not increase the amplitude of the MMN. This is compatible with the findings of Bendixen and Schröger (2008), but extends this pattern of results to concrete rule paradigms.

The current results may also reveal important information on how models are formed in auditory sensory memory. While MMN amplitude did not vary with deviant probability when using the double deviant pattern, it was significantly attenuated in the single deviant pattern when the deviant occurred relatively frequently. At this high probability of occurrence, the global rules dictating the single deviant pattern are changed quite often, on average every 3 seconds. This seems to imply that pre-conscious auditory models are poorly established by local rules alone. Global rules appear to be crucial for their predictive power. Alternatively, in the high probability single pattern condition, it is possible that two representations of global rules are formed (e.g., every second tone is B, and every second tone is A). Under these circumstances, repetition deviants may be found to be a memory "match" rather than "mismatch" because they conform to one of these global rules.

The idea that MMN amplitude varies with the strength of the sensory memory trace, and that this property underlies the effect of deviant probability on MMN amplitude, has been a critical assumption in some research on the structure of auditory memory (Deacon, Nousak, Pilotti, Ritter, & Yang, 1998; Molholm, Gomes, Lobosco, Deacon, & Ritter, 2004; Grimm & Schröger, 2007), and the neural pathology of schizophrenia (Javitt et al., 1998; Shelley et al., 1999; Sato, et al., 2003). The current results suggest that this assumption may not be justified. Other effects that are thought to be mediated by the strength of the memory for the standard stimulus, such as augmentation of the MMN with attention (Muller-Gass, Stelmack, & Campbell, 2006; Szymanski, Yund, & Woods, 1999; Alain & Woods, 1997), may also require reinterpretation.

Nevertheless, it remains possible that the MMN to pattern violations has a different relationship with deviant probability than does the MMN to oddball deviants. In addition to being based on higher-level rules, and not simple features, the MMN to violations of a two-tone alternating pattern has a slightly more central scalp distribution than the MMN to oddball frequency deviants, suggesting that its sources are distinct (Alain, Achim, & Woods, 1999). Future investigations of the effects of deviant probability on MMN amplitude in an oddball sequence using deviants that do not appear to cause N1 enhancement, such as intensity decrements (Jacobsen, Horenkamp, & Schröger, 2003), or decreases in duration (Jacobsen & Schröger, 2003), may be useful in clarifying this issue.

Figure Caption

Figure 1: Grand average difference waves for Experiment 1, under all conditions. In both the oddball paradigm, and the patterned paradigm, a large amplitude, fronto-central MMN is apparent at about 190 ms. These MMNs clearly invert in polarity at the mastoid in both conditions. In the oddball paradigm, the amplitude of the MMN was smaller in the high deviant probability condition than the rare deviant probability condition, but this difference only reached significance at the mastoid. In the pattern paradigm, the reduction of the MMN at high deviant probability was significant at both Fz and M1.

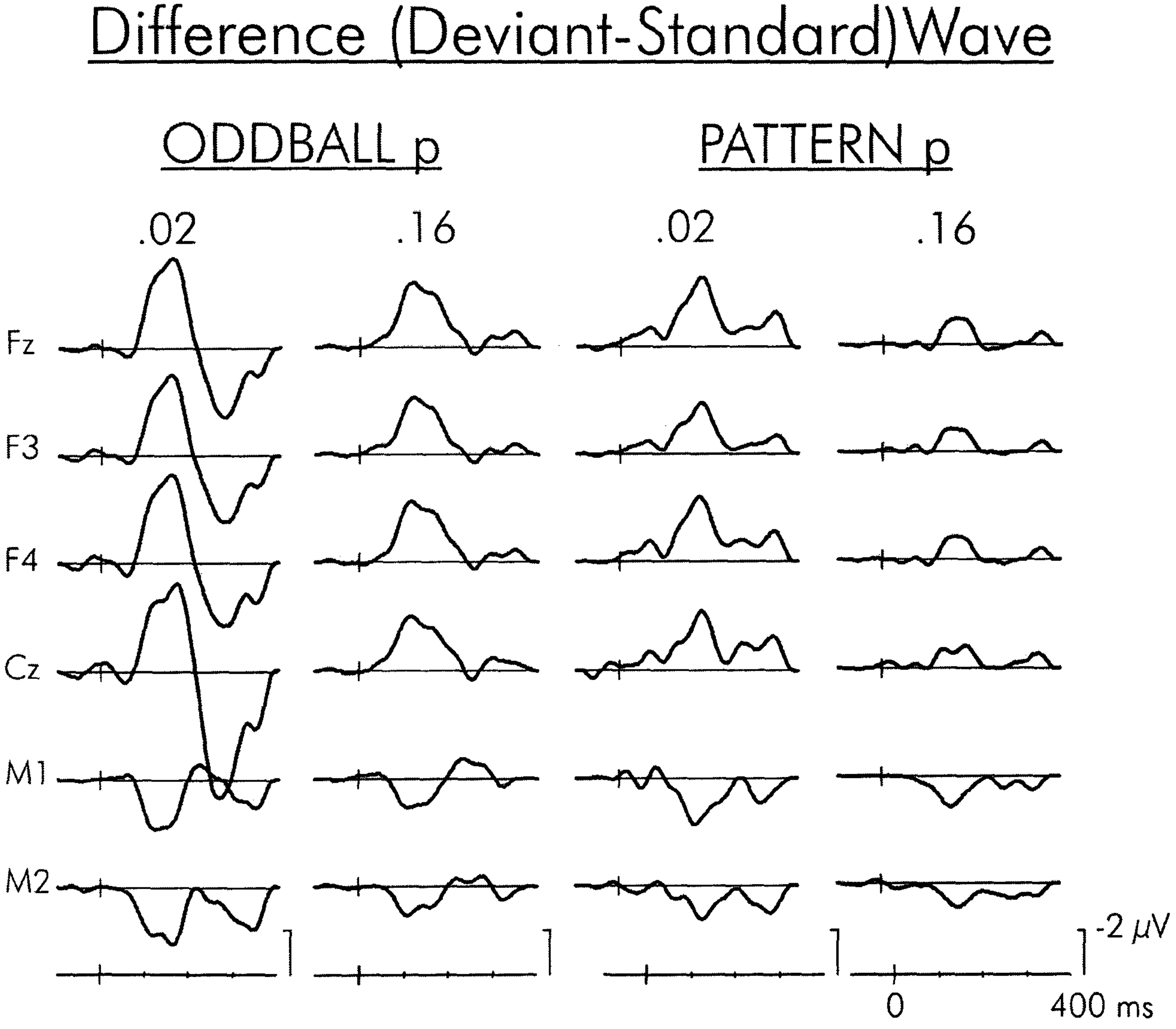

Figure Caption

Figure 2: An illustration of the differences between the single deviant pattern employed in Experiment 1, and the double deviant pattern used in Experiment 2. Every second tone is coloured gray. Note that in the single deviant pattern, following a pattern violation, the identity of the tones coloured gray changes (e.g., from B to A, or from A to B). In contrast, in the double deviant pattern, the identity of the gray tones is consistent for all standard stimuli.

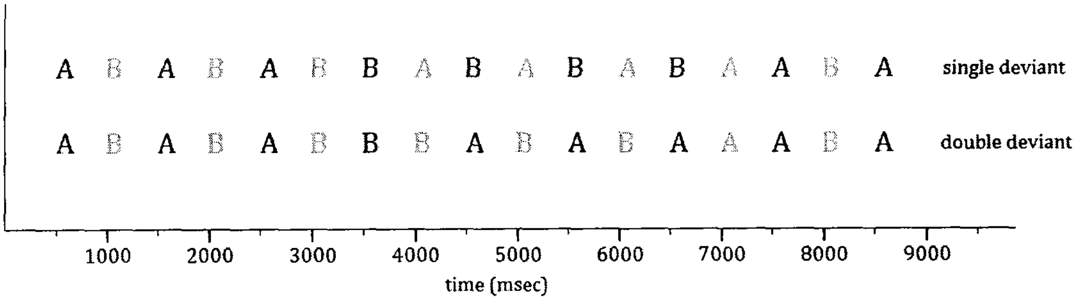

Figure Caption

Figure 3: Grand average difference waves for Experiment 2, under all conditions. In all probability conditions, a large amplitude, fronto-central MMN is apparent at about 200 ms. This MMN clearly inverts in polarity at the mastoid. Although some small, non-systematic variations in amplitude are visible for the MMN, there was no significant effect of deviant probability ($F < 1$ at both M1 and Fz).

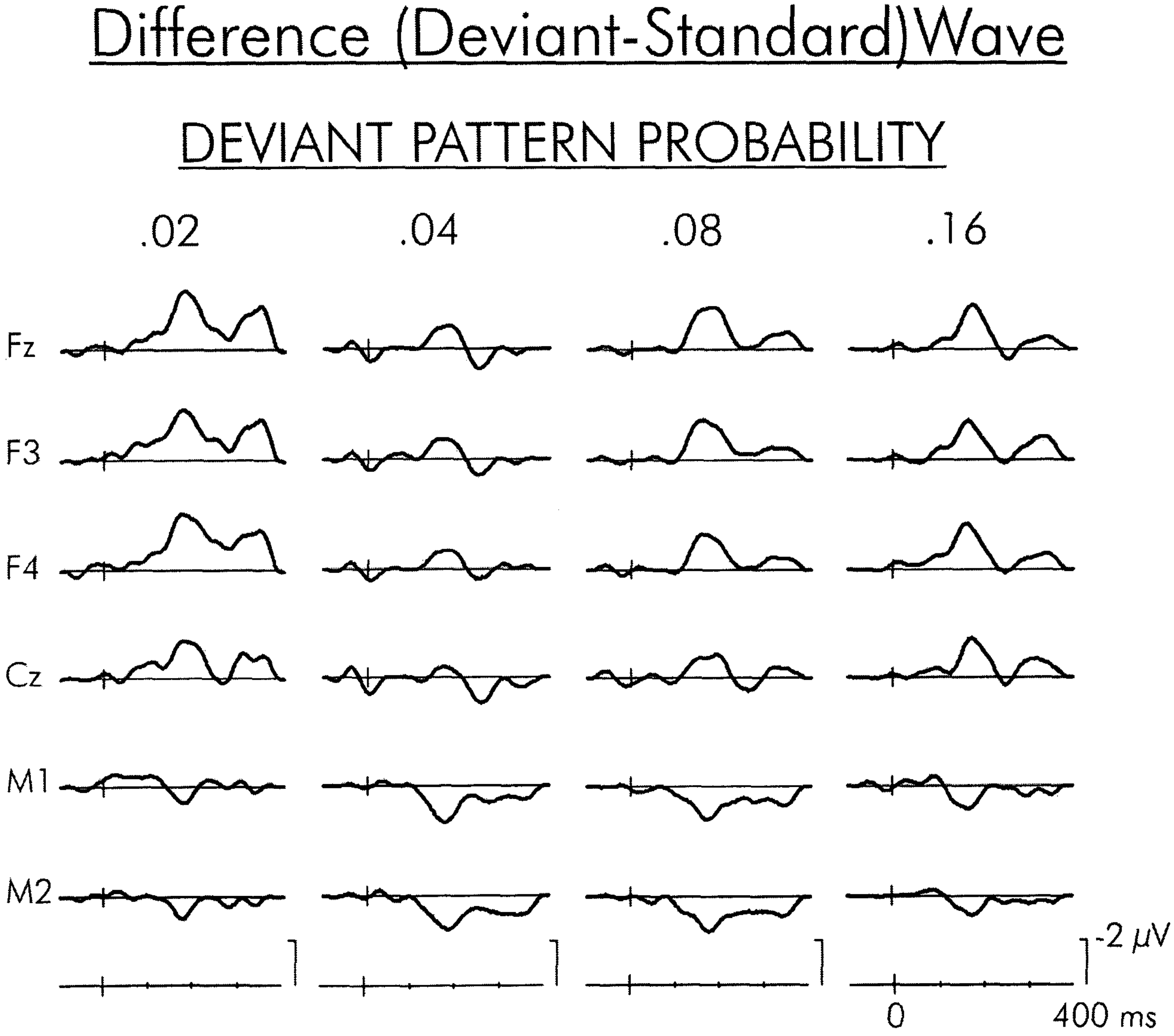

Table 1: Means and standard errors of the means (in parentheses) of MMN amplitude at Fz and M1 under all probability conditions in Experiments 1 and 2.

	Study 1 (oddball)		Study 1 (single deviant)		Study 2 (double deviant)	
	Fz	M1	Fz	M1	Fz	M1
High, $p = 0.16$	-2.63 (0.44)	1.28 (0.21)	-1.14 (0.46)	1.14 (0.16)	-1.75 (0.15)	1.11 (0.28)
Moderate, $p = 0.08$	-	-	-	-	-1.88 (0.58)	1.13 (0.37)
Low, $p = 0.04$	-	-	-	-	-1.27 (0.75)	1.64 (0.34)
Rare, $p = 0.02$	-3.95 (0.81)	2.12 (0.39)	-2.43 (0.61)	1.94 (0.44)	-2.41 (0.61)	1.12 (0.43)

Table 2: Summary of behavioural results from Experiment 3. Hit rate (HR), reaction time (RT), standard deviation of response time (SDRT), and false alarms (FA) are listed as means and standard errors of the means (in parentheses).

	Single Deviant Pattern		Double Deviant Pattern	
	High *p*	Rare *p*	High *p*	Rare *p*
HR	0.92 (0.03)	0.98 (0.01)	0.97 (0.01)	0.99 (0.01)
RT (msec)	446 (15)	498 (10)	490 (29)	510 (17)
SDRT (msec)	108 (18)	95 (9)	136 (18)	108 (13)
FAs (total #)	0.3 (0.2)	3.1 (0.6)	0.4 (0.2)	2.3 (0.5)

Chapter 5

Summary and Conclusions

The present thesis sought to examine the automaticity of the auditory MMN. Three studies were performed that took direct and indirect approaches to this problem. In the first study, the automaticity of the detection of auditory pattern violations was examined by varying the presumed attentional demands of a to-be-attended visual task. In the second study, automaticity was examined more directly by examining the detection of auditory pattern violations during conscious and unconscious states (the waking and sleeping states, respectively). In the third experiment, automaticity was examined indirectly by manipulating the probability of occurrence of the pattern-violating deviants. Probability of occurrence of the deviant is thought to affect the strength of the sensory memory for the auditory past. However, the memory formation and comparison processes that underlie the MMN are operations that are claimed to occur automatically.

Automaticity, as defined by Posner and Snyder (1975a,b), and later modified by Kahneman and Treisman (1984), is a very useful concept in the study of attention. In structural models of attention, automatic mechanisms precede the bottleneck that separates pre-conscious from conscious processing. One important recent model of attention and information processing is that of Näätänen, which was the first to employ evidence from ERP research (Näätänen, 1990). The present thesis was carried out within the framework of his model.

Näätänen's model describes 3 routes to conscious awareness: one task-dependent route, and two task-independent routes. The task-dependent route is associated with "active" or "voluntary" attention, and is indexed by the PN. Two task-independent routes are associated with "passive" or "involuntary" attention. Processing in these routes is thus claimed to occur independently of attention and the demands of ongoing cognitive activity (i.e., what the subject "is doing"). The first of these routes is indexed by the N1 component of the auditory ERP, and handles abrupt (or "transient") changes in the energy of the acoustic environment. The second route, indexed by the MMN, handles more complex changes in the environment – the violation of rules or invariances that have been extracted from the recent acoustic past. The MMN is intimately tied to the contents of sensory memory, and as such, can provide a unique window to view how auditory information is processed in the absence of attention. In his model, Näätänen proposed that attentional selection took place at a fairly late stage of processing: the physical features of stimuli are extracted, and synthesized into auditory sensory memory at the pre-conscious level. This statement was largely based on the fact that the MMN to even very small deviants could be elicited under passive conditions (i.e., in the absence of attention). If the processes that underlie the MMN, such as memory formation, were not carried out automatically, an MMN would not be observed to unattended deviants. Näätänen placed special importance on the MMN, and as such, the automaticity of the MMN became an important question in the study of attention. Its automaticity is also a crucial concern for clinical and applied research that employs the MMN.

Much of the research that tested the automaticity of the MMN was carried out using oddball paradigms. In the oddball paradigm, a deviant is often created by changing a *physical* feature of the standard. This physical change risks the possibility that the deviant stimulus activates fresh neuronal populations in the auditory cortex. Since the N1 component of the ERP is tied to the refractoriness of afferent neurons, the deviance-related negativity (DRN) that is recorded over fronto-central areas of the scalp under such circumstances reflects a composite of two negativities, the "true" MMN and N1 enhancement. This is especially true of oddball paradigms with tonal frequency deviants (Jacobsen & Schröger, 2001), which have been used in much of the research studying the automaticity of the MMN. Consequently, the results obtained in this research may be attributable to N1, rather than the MMN. N1 is only related in part to the contents of sensory memory, and has several underlying components, some of which appear to serve a non modality-specific alerting function, rather than an auditory-specific information processing one (Näätänen & Picton, 1987). Modulation of a non-modal alerting mechanism would certainly have few implications for the detection of auditory change as reflected by the MMN, yet research using frequency oddball paradigms risks making this claim.

To avoid this problem, the present thesis employed a two-tone alternating pattern. Violations of this alternating pattern were created by repeating the same stimulus. Since deviants in this kind of sequence are physically identical to the standards that precede them, there should be no fresh afferent activation. If anything, the N1 to such a deviant should be smaller than that to the standard (Butler, 1968), and as a result, the DRN should be composed solely of the "true" MMN. In the present thesis, two-tone alternating patterns were employed to study the automaticity of the MMN in three different, but complementary, experimental paradigms.

In Study 1 (Sculthorpe et al., 2008) the automaticity of the MMN was tested by an attentional manipulation. A strongly automatic process should be unaffected by the direction and/or strength of attention, while a weakly automatic one may be influenced, but never eliminated, by it (Hackley, 1993). Many different experimental paradigms have been used to study the effect of attention on the MMN. For the purpose of the present thesis, these were described as direction of attention and strength of attention studies. Both types of paradigms can be carried out in an intramodal or an intermodal fashion. Much of the cited evidence for reduction, and even elimination, of the MMN in the absence of attention has come from intramodal direction of attention studies, usually involving dichotic listening. However, when an auditory channel is attended, the detection of the rare deviant (or "target") will elicit another component called N2b, which can also overlap both temporally and spatially with the MMN. Dichotic listening studies also risk feature-specific competition, a phenomenon that exists due to the limited processing capacity of the comparator mechanism underlying the MMN. As such, the results of intramodal direction of attention studies can be attributed to mechanisms other than the enhancement of the MMN by attention.

Strength of attention studies, in which attention is never directed towards the MMN-eliciting auditory channel, but the difficulty of a diversion task is manipulated, do not risk these confounds. As such, this type of paradigm is extremely useful to study the automaticity of the MMN. Very few strength of attention studies have demonstrated modulation of the MMN with active task demands. Those that have done so used a continuous visual task, but also, unfortunately, employed moderate or large tonal frequency deviants in an oddball paradigm. As mentioned previously, using these types of deviants makes it likely that the DRN will receive contributions from N1 enhancement. It was therefore unknown whether the manipulation of the attentional demands of a continuous visual task would, indeed, affect the MMN, rather than the overlapping N1 enhancement. Study 1, therefore, employed a continuous visual task at two levels of difficulty while subjects ignored a concurrently-presented auditory pattern that was unrelated to the visuospatial tracking task. The two-tone alternating pattern was presented in two different conditions, in which the constituent tones of the pattern were separated by 1 or 6 semitones. This manipulation tested the possibility that the small MMNs elicited by less perceptible deviants might be more susceptible to attention. In addition to the two levels of the visuospatial tracking task (easy and difficult), a reading condition was also employed, in which subjects ignored the auditory sequence and read a self-selected book. Despite large differences in performance between the easy and the difficult task, which confirmed that task difficulty was successfully manipulated, the amplitude of the MMN was not significantly different in any of the task conditions. These results were obtained in both the 1- and the 6-semitone condition, and suggest that the MMN is at least weakly automatic.

Processes that are automatic are carried out at the pre-conscious level, and as such, should be present even in unconscious states. Numerous studies, therefore, have examined whether an MMN can be elicited in unconscious states, most often natural sleep, but also states such as coma and anaesthesia. Most of these studies employed oddball paradigms with tonal frequency deviants. Study 2 (Sculthorpe, Ouellet, et al., 2009) sought to determine whether the MMN to pattern violations could be observed in natural sleep. To date, three sleep studies have been conducted using auditory sequences that should have avoided N1 enhancement. Intensity decrement deviants in an oddball paradigm have failed to demonstrate an MMN during sleep (Loewy, Campbell, de Lugt, Elton, & Kok, 2000; Macdonald, Jamshidi, & Campbell, 2008), but duration decrements have been used to demonstrate an MMN in every stage of sleep except stage 4 (Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008). Varying the duration of a stimulus can, however, have subtle effects on the power (or intensity) of the stimulus. This is especially the case when the duration of stimuli is decreased to be less than 200 ms, as was done by Ruby and colleagues. This may result in a differential perception of intensity between the standard and the deviant, thus causing the standard and deviant to activate distinct neuronal populations in ampliotopically-organized cortex. Although intensity decrement deviants in an oddball paradigm avoid N1 enhancement, the possible involvement of distinct afferent neuronal populations for the standard and deviant implies that the detection of deviance would not necessarily require the memory comparison process that is central to the classic description of the MMN.

In Study 2, the two-tone alternating pattern was presented under a passive condition (reading) in a conscious waking state, as well as during an unconscious state, natural sleep. As was the case in Study 1, Study 2 employed two auditory conditions, in which the constituent tones of the pattern were separated by 1 or 6 semitones. The more perceptible deviants in the 6 semitone condition elicited an MMN both in the waking state, *and* during REM sleep. Deviants in the 1 semitone condition elicited an MMN only in the waking state. No MMN was observed during NREM sleep, even in the 6 semitone condition. The amplitude of the MMN observed in REM sleep in the 6 semitone condition was not significantly different from the amplitude of the MMN obtained in the waking state. Despite the fact that a significant MMN was not observed to the less perceptible 1 semitone condition deviants in REM sleep, the presence of an MMN to deviants in the more perceptible 6 semitone condition pattern indicates that MMN generation occurs at a pre-conscious level, and as such, is at least weakly automatic.

Interpreted in isolation, the results of Studies 1 and 2 could indicate that the MMN to pattern violations is strongly automatic: the operations required to detect auditory pattern violations function at the pre-conscious level, and are unaffected by the attentional demands of an active visual task. From a practical point of view, this makes the pattern MMN especially desirable for use in clinical and applied research. Indeed, the pattern MMN was recently employed to provide the first demonstration of pre-attentive processing differences between individuals with high and low psychometric intelligence (Sculthorpe, Stelmack, & Campbell, 2009).

Some experimenters, however, claim to have demonstrated genuine effects of attention on the MMN. In general, these studies have shown enhancement of the MMN with attention. The proposed mechanism of this weak automaticity is that attention enhances the MMN by increasing the strength and/or precision of the memory for the standard stimulus (Muller-Gass, Stelmack, & Campbell, 2006; Alain & Woods, 1997; Szymanski, Yund, & Woods, 1999). Study 3 approached this proposed mechanism for weak automaticity of the MMN in a somewhat indirect fashion, by examining the relationship between the strength of the memory for the standard stimulus and the amplitude of the MMN. Several lines of research have demonstrated an apparent link between the amplitude of the MMN and the strength of the underlying sensory memory. One popular method is to vary the number of standard stimuli presented between successive deviants, since additional repetitions of the standard presumably strengthen its memory representation (Imada, Hari, Loveless, McEvoy, & Sams, 1993). Much of the evidence demonstrating increased MMN amplitude when the number of standards is increased derives from studies manipulating deviant probability. Probability studies have typically reported that the MMN increases in amplitude as deviant probability decreases (Näätänen, Sams, Järvilehto, & Soininen, 1982; Sinkkonen, Kaski, Huotilainen, Ilmoniemi, Näätänen, & Kaila, 1996; Javitt, Grochowski, Shelley, & Ritter, 1998; Shelley, Silipo, & Javitt, 1999; Sabri & Campbell, 2001; Sato, et al., 2000; Sato, et al., 2003). These studies, however, used oddball paradigms that invited N1 enhancement following presentation of the deviant, raising the possibility that the observed modulation of the MMN may be an artefact of varying the contribution of N1 enhancement to the DRN. The amplitude of N1 increases dramatically when the time between stimulus presentations increases. Thus, as the time between deviant presentations increases, the resulting increased negativity that is apparent over fronto-central areas of the scalp may reflect an enhancement of the MMN, or an enhancement of the N1.

Study 3, therefore, used a two-tone alternating pattern to investigate the effect of deviant probability on the MMN. Since no differential effects were expected between small and large MMNs, the frequency separation between the two constituent tones of the pattern was fixed at 6 semitones. Study 3 consisted of three experiments. Experiment 1 presented both an oddball and a patterned auditory sequence at high and rare deviant probability. In both conditions, the amplitude of the MMN was larger in the rare than the high probability condition. This could be taken as convincing evidence that the MMN is indeed affected by the probability of occurrence of the deviant. There exists, however, an important alternative explanation. The MMN is also affected by the perceptibility of the deviant. When deviant stimuli are presented a high probability in the single deviant pattern used in Experiment 1, the global rules that represent the pattern in sensory memory are changed relatively often. The lack of a stable representation of the standard pattern in sensory memory may make perception of the deviant more difficult. Thus, in Experiment 2, a variation of the two-tone pattern was used that should have preserved global rules in the pattern following deviant occurrence, the double deviant pattern. The double deviant pattern was presented at four probability levels (high, moderare, low, and rare). In Experiment 2, even when deviants were delivered relatively frequently, the representation of the standard pattern in sensory memory should have remained stable. In this case, MMN amplitude did not vary with probability. Thus, when the perceptibility of the deviant is controlled, manipulating the probability of deviant occurrence does not affect the amplitude of the MMN, contrary to claims made in the classic MMN model.

Deviant perceptibility could, however, only be inferred in Experiments 1 and 2. Experiment 3, therefore, employed a behavioural study that examined the accuracy with which subjects could actually detect deviant repetitions, thus providing a measure of deviant perceptibility. The patterns used in Experiments 1 and 2 (single and double deviant patterns, respectively) were both presented at two levels of deviant probability, high and rare. As predicted, the performance results demonstrated that in the single deviant pattern, deviant perceptibility was influenced by deviant probability. As such, the apparent probability effects observed in the pattern condition of Experiment 1 could be attributable to deviant perceptibility. Conversely, deviant perceptibility was unaffected by deviant probability when using the pattern from Experiment 2. As such, Experiment 2 examined deviant probability without the confounding influence of deviant perceptibility. In Experiment 2, MMN amplitude did not vary with deviant probability. As such, it appears that the amplitude of the MMN does not vary with the strength of the underlying memory representation.

If the MMN is indeed weakly automatic, and enhanced by attention, the results of Study 3 suggest that the underlying effect is not an increase in the strength of the memory for the standard. Those studies that have demonstrated an effect of attention on the amplitude of the MMN, therefore, might be explained by some other mechanism (e.g., N2b overlap, feature-specific competition), might be a result of the modulation of N1 rather than MMN, or might in fact be demonstrating an attention-related enhancement in the precision of the memory for the standard. Indeed, attention-related changes in the precision of sensory encoding are an under-studied process in human auditory research that may have great explanatory power in understanding selective attention (for discussions of this concept in both human and animal research, see Giard, Collet, Bouchet, & Pernier, 1994; de Boer & Thornton, 2007; Spitzer, Desimone, & Moran, 1988; Fritz, Shamma, Elhilali, & Klein, 2003; Ozaki, Jin, Suzuki, Baba, Matsunaga, & Hashimoto, 2004; Kauramäki, Jääskeläinen, & Sams, 2007).

The ability to selectively focus, and optimize goal-directed behaviour, while maintaining responsiveness to environmental events that occur outside that focus is a powerful feature of human cognition. Without this ability, the continuous sense of self and focused thought that makes up the human experience of consciousness would not be possible. The mechanisms that maintain sensitivity to changes in the environment in the presence of selective, voluntary focus are pre-conscious systems that process large quantities of stimuli even before the awareness of stimulus onset emerges. Among these pre-conscious systems is the change detection system underlying the MMN: a sophisticated novelty detector that extracts invariances from the recent acoustic past, and determines whether incoming auditory stimuli conform to those regularities. The results of the present thesis indicate that the operations of this novelty detector are quite automatic. They occur even during very demanding visual tasks requiring continuous, uninterrupted attention, and even continue to function during REM sleep. While there are many researchers who claim to have demonstrated a genuine effect of attention on the MMN, we now also know that it is unlikely that these effects are mediated by attention strengthening sensory memory. Future research should examine the many potential mechanisms of selective attention, and the MMN, no doubt, will continue to play an important role in these investigations. The discrepancies between the findings of the present thesis and the established MMN literature, however, should be taken as an important warning for the careful selection of MMN paradigms that avoid fresh afferent activation in these future endeavours. As such, patterned auditory stimuli may have an important long-term role to play in the study of human selective attention.

References

Aitkin, L. M., & Webster, W. R. (1971). Tonotopic organization in the medial geniculate body of the cat. *Brain Res., 26*, 402-405.

Alain, C., Achim, A., & Woods, D. L. (1999). Separate memory-related processing for auditory frequency and patterns. *Psychophysiology, 36*(6), 737-744.

Alain, C., & Izenberg, A. (2003). Effects of attentional load on auditory scene analysis. *J. Cogn. Neurosci., 15*(7), 1063-1073.

Alain, C., & Woods, D. L. (1997). Attention modulates auditory pattern memory as indexed by event-related potentials. *Psychophysiology, 34*, 534-546.

Alain, C., Woods, D. L., & Ogawa, K. H. (1994). Brain indices of automatic pattern processing. *NeuroReport, 6*, 140-144.

Alho, K., Sams, M., Paavilainen, P., Reinikainen, K., & Näätänen, R. (1989). Event-related brain potentials reflecting processing of relevant and irrelevant stimuli during selective listening. *Psychophysiology, 26*(5), 514-528.

Alho, K. (1995). Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear Hear. 16*, 38-51.

Alho, K., Sams, M., Paavilainen, P., Reinikainen, K., & Näätänen,R. (1989). Event-related brain potentials reflecting processing of relevant and irrelevant stimuli during selective listening. *Psychophysiology, 26*, 514-528.

Alho, K., & Sinervo, N. (1997). Preattentive processing of complex sounds in the human brain. *Neurosci. Lett., 233*, 33-36.

Alho, K., Töttölä, K., Rein ikainen, K., Sams, M., & Näätänen, R. (1987). Brain mechanisms of selective listening reflected by event-related potentials. *Electroencephalogr. Clin. Neurophysiol., 68*, 458-470.

Alho, K., Woods, D. L., & Algazi, A. (1994). Processing of auditory stimuli during auditory and visual attention as revealed by event-related potentials. *Psychophysiology, 31*, 469-479.

Alho, K., Woods, D. L., Algazi, A., & Näätänen, R. (1992). Intermodal selective attention. II. Effects of attentional load on processing of auditory and visual stimuli in central space. *Electroencephalogr. Clin. Neurophysiol., 82*, 356-368.

Amadeo, M., & Shagass, C. (1973). Brief latency click-evoked potentials during waking and sleep in man. *Psychophysiology, 10*(3), 244-250.

Arnott, S. R., & Alain, C. (2002). Stepping out of the spotlight: MMN attenuation as a function of distance from the attended location. *NeuroReport, 13*(17), 2209-2212.

Atienza, M., & Cantero, J. L. (2001). Complex sound processing during human REM sleep by recovering information from long-term memory as revealed by the mismatch negativity (MMN). *Brain Res., 901*(1-2), 151-160.

Atienza, M., Cantero, J. L., & Dominguez-Marin, E. (2002). The time course of neural changes underlying auditory perceptual learning. *Learn. Mem., 9*(3), 138-150.

Atienza, M., Cantero, J. L., & Gómez, C. M. (1997). The mismatch negativity component reveals the sensory memory during REM sleep in humans. *Neurosci. Lett., 237*(1), 21-24.

Atienza, M., Cantero, J. L., & Gómez, C. M. (2000). Decay time of the auditory sensory memory trace during wakefulness and REM sleep. *Psychophysiology, 37*(4), 485-493.

Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophr. Res., 69*, 203-217.

Bastien, C., & Campbell, K. (1992). The evoked K-complex: All-or-none phenomenon? *Sleep, 15*(3), 236-245.

Bastuji, H., Garcia Larrea, L., Bertrand, O., & Mauguière, F. (1988). BAEP latency changes during nocturnal sleep are not correlated with sleep stages but with body temperature variations. *Electroencephalogr. Clin. Neurophysiol., 70*(1), 9-15.

Bendixen, A., & Schröger, E. (2008). Memory trace formation for abstract auditory features and its consequences in different attentional contexts. *Biol. Psychol., 78*, 231-241.

Berti, S., & Schröger, E. (2003). Working memory controls involuntary attention switching: evidence from an auditory distraction paradigm. *Eur. J. Neurosci., 17*, 1119-1122.

Bilecen, D., Seifritz, E., Scheffler, K., Henning, J., & Schulte, A.-C. (2002). Amplitopicity of the human auditory cortex: An fMRI study. *NeuroImage, 17*, 710-718.

Boudreau, J. C., & Tsuchitani, C. (1968). Binaural interaction in the cat superior olive S segment. *J. Physiol., 31*(3), 442-454.

Broadbent, D. E. (1958). *Perception and Communication.* London: Pergamon.

Brownell, W. E., Bader, C. R., Bertrand, D., & de Ribaupierre, Y. (1985). Evoked mechanical responses of isolated cochlear outer hair cells. *Science, 227*(4683), 194-196.

Butler, R. A. (1968). Effect of changes in stimulus frequency and intensity on habituation of the human vertex potential. *J. Acoust. Soc. Am., 44*(4), 945-950.

Campbell, K. B., & Bartoli, E. A. (1986). Human auditory evoked potentials during natural sleep: The early components. *Electroencephalogr. Clin. Neurophysiol., 65*(2), 142-149.

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

Campbell, K.B., & Colrain, I.M. (2002). Event-related potential measures of the inhibition of information processing: II. The sleep onset period. *Int. J. Psychophysiol., 46*, 197-214.

Carr, C. E., & Konishi, M. (1988). Axonal delay lines for time measurement in the owl's brainstem. *Proc. Natl. Acad. Sci. U.S.A., 85*, 8311-8315.

Celesia, G. G. (1976). Organization of auditory cortical areas in man. *Brain, 99*, 403-414.

Cherry, E. C. (1953). Some experiments on the recognition of speech, with one and with two ears. *J. Acoust. Soc. Am., 25*(5), 975-979.

Cody, A. R., & Russell, I. J. (1987). The responses of hair cells in the basal turn of the guinea-pig cochlea to tones. *J. Physiol., 383*, 551-569.

Colrain, I.M., & Campbell, K.B. (2007). The use of evoked potentials in sleep research. *Sleep Med. Rev., 11*, 277-293.

Connolly, J. F., Aubry, K., McGillivary, N., & Scott, D. W. (1989). Human brainstem auditory evoked potentials fail to provide evidence of efferent modulation of auditory input during attentional tasks. *Psychophysiology, 26*(3), 292-303.

Cote, K. A. (2002). Probing awareness during sleep with the auditory odd-ball paradigm. *Int. J. Psychophysiol., 46*(3), 227-241.

Cote, K.A., & Campbell, K.B., (1999). P300 to high intensity stimuli during REM sleep. *Clin. Neurophysiol., 110*, 1345-1350.

Cote, K. A., de Lugt, D. R., Langley, S. D., & Campbell, K. B. (1999). Scalp topography of the auditory evoked K-complex in stage 2 and slow wave sleep. *J. Sleep Res., 8*(4), 263-272.

Cote, K.A., Etienne, L., & Campbell, K.B. (2001). Neurophysiological evidence for the detection of external stimuli during sleep. *Sleep, 24*, 791-803.

Cowan, N. (1984). On short and long auditory stores. *Psychol. Bull., 96*, 341-370.

Cowan, N., Winkler, I., Teder, W., & Näätänen, R. (1993). Memory prerequesites of mismatch negativity in the auditory event-related potential (ERP). *J. Exp. Psychol. Learn. Mem. Cogn., 19*(4), 909-921.

Crowley, K. E., & Colrain, I. M. (2004). A review of the evidence for P2 being an independent component process: Age, sleep and modality. *Clin. Neurophysiol., 115*, 732-744.

Davis, A. E., & Beagley, H. A. (1985). Acoustic brainstem responses for clinical use: The effect of attention. *Clin. Otolaryngol., 10*, 311-314.

Davis, H., & Zerlin, S. (1966). Acoustic relations of the human vertex potential. *J. Acoust. Soc. Am., 39*, 109-116.

Davis, H., Davis, P. A., Loomis, A. L., Harvey, E. N., & Hobart, G. (1939). Electrical reactions of the human brain to auditory stimulation during sleep. *J. Neurophysiol., 2*, 500-514.

de Boer, J., & Thornton, A. R. (2007). Effect of subject task on contralateral suppresion of click evoked otoacoustic emissions. *Hear. Res., 233*, 117-123.

de Lugt, D. R., Loewy, D. H., & Campbell, K. B. (1996). The effect of sleep onset on event related potentials with rapid rates of stimulus presentation. *Electroencephalogr. Clin. Neurophysiol., 98*(6), 484-492.

Deacon, D., Nousak, J. M., Pilotti, M., Ritter, W., & Yang, C.-M. (1998). Automatic change detection: Does the auditory system use representations of individual stimulus features or gestalts? *Psychophysiology, 35*, 413-419.

Deacon-Elliott, D., Bell, I., & Campbell, K. B. (1987). Estimation of auditory threshold during sleep using brainstem auditory-evoked potentials. *Audiology, 26*(6), 363-368.

Deouell, L.Y. (2007). The frontal generator of the mismatch negativity revisited. *J. Psychophysiol., 21*, 188-203.

Descartes, R. (1649). A Discourse of a Method for the Well Guiding of Reason and the Discovery of Truth in the Sciences. Early English Books Online: http://gateway.proquest.com.proxy.bib.uottawa.ca/openurl?ctx_ver=Z39.88-2003&res_id=xri:eebo&rft_id=xri:eebo:image:54569

Deutsch, J. A., & Deutsch, D. (1963). Attention: Some theoretical considerations. *Psychol. Rev., 70*(1), 80-90.

Dittmann-Balcar, A., Thienel, R., & Schall, U. (1999). Attention-dependent allocation of auditory processing resources as measured by mismatch negativity. *NeuroReport, 10*, 3749-3753.

Donald, M. W., & Young, M. J. (1982). A time-course analysis of attentional tuning of the auditory evoked response. *Exp. Brain Res., 46*, 357-367.

Donchin, E. (1981). Surprise!....Surprise? *Psychophysiology, 18*, 493-513.

Donchin, E., Ritter, W., & McCallum, W. C. (1978). Cognitive psychophysiology: The endogenous components of the ERP. In E. Callaway, P. Tueting, & S. H. Koslow (Eds.), *Event-Related Brain Potentials in Man* (pp. 349-441). New York: Academic Press.

Dyson, B. J., Alain, C., & He, Y. (2005). Effects of visual attentional load on low-level auditory scene analysis. *Cogn. Affect. Behav. Neurosci., 5*(3), 319-338.

Escera, C., Alho, K., Schröger, E., & Winkler, I. (2000). Involuntary attention and distractibility as evaluated with event-related brain potentials. *Audiol. Neuro-otol., 5*, 151-166.

Escera, C., Alho, K., Winkler, I., & Näätänen, R., (1998). Neural mechanisms of involuntary attention to acoustic novelty and change. *J. Cogn. Neurosci., 10*, 590-604.

Fischer, C., Luauté, J., Adeleine, P., & Morlet, D. (2004). Predictive value of sensory and cognitive evoked potentials for awakening from coma. *Neurology, 63*(4), 669-673.

Fischer, C., Morlet, D., Bouchet, P., Luaute, J., Jourdan, C., & Salord, F. (1999). Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin. Neurophysiol., 110*(9), 1601-1610.

Fischer, C., Morlet, D., & Giard, M. (2000). Mismatch negativity and N100 in comatose patients. *Audiol. Neuro-otol., 5*(3-4), 192-197.

Fritz, J., Shamma, S., Elhilali, M., & Klein, D. (2003). Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex. *Nat. Neurosci., 6*(11), 1216-1223.

Fujiwara, N., Nagamine, T., Imai, M., Tanaka, T., & Shibasaki, H. (1998). Role of the primary auditory cortex in auditory selective attention studied by whole-head neuromagnetometer. *Cogn. Brain Res., 7*, 99-109.

Giard, M.-H., Collet, L., Bouchet, P., & Pernier, J. (1994). Auditory selective attention in the human cochlea. *Brain Res.*, *633*, 353-356.

Giard, M.-H., Perrin, F., Pernier, J., & Bouchet, P. (1990). Brain generators implicated in the processing of auditory stimulus deviance: A topographic event-related potential study. *Psychophysiology, 27*(6), 627-640.

Gomes, H., Bernstein, R., Ritter, W., Vaughan, H. G., & Miller, J. (1997). Storage of feature conjunctions in transient auditory memory. *Psychophysiology, 34*(6), 712-716.

Gomes, H., Ritter, W., & Vaughan, H. G. (1995). The nature of pre-attentive storage in the auditory system. *J. Cogn. Neurosci., 7*, 81-94.

Grimm, S., & Schröger, E. (2007). The processing of frequency deviations within sounds: Evidence for the predictive nature of the Mismatch Negativity (MMN) system. *Restor. Neurol. Neurosci.*, *25*, 241-249.

Guillery, R. W., Feig, S. L., & Lozsádi, D. A. (1998). Paying attention to the thalamic reticular nucleus. *Trends Neurosci., 21*(1), 28-32.

Hackley, S. A. (1993). An evaluation of the automaticity of sensory processing using event-related potentials and brain-stem reflexes. *Psychophysiology, 30*, 415-428.

Hackley, S. A., Woldorff, M., & Hillyard, S. A. (1987). Combined use of microreflexes and event-related brain potentials as measures of auditory selective attention. *Psychophysiology, 24*(6), 632-647.

Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography -- Theory, instrumentation, and application to noninvasive studies of the working human brain. *Review of Modern Physics, 65*, 413-497.

Hansen, J. C., & Hillyard, S. A. (1980). Endogenous brain potentials associated with selective auditory attention. *Electroencephalogr. Clin. Neurophysiol., 49*, 277-290.

Hari, R., Kaila, K., Katila, T., Tuomisto, T., & Varpula, T. (1982). Interstimulus interval dependence of the auditory vertex response and its magnetic counterpart: Implications for their neural generation. *Electroencephalogr. Clin. Neurophysiol., 54*, 561-569.

Harmony, T., Bernal, J., Fernández, T., Silva-Pereyra, J., Fernández-Bouzas, A., Marosi, E., et al. (2000). Primary task demands modulate P3a amplitude. *Cogn. Brain Res., 9*, 53-60.

Hernández-Peón, R., Scherrer, H., & Jouvet, M. (1956). Modification of electric activity in cochlear nucleus during "attention" in unanesthetized cats. *Science, 123*(3191), 331-332.

Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science, 182*(4108), 177-180.

Hillyard, S. A., Woldorff, M., Mangun, G. R., & Hansen, J. C. (1987). Mechanisms of early selective attention in auditory and visual modalities. In R. J. Ellingson, N. M. Murray, & A. M. Halliday (Eds.), *The London Symposia (EEG Suppl. 39)* (pp. 317-324). Amsterdam: Elsevier.

Horváth, J., Czigler, I., Jacobsen, T., Maess, B., Schröger, E., & Winkler, I. (2008). MMN or no MMN: No magnitude of deviance effect on the MMN amplitude. *Psychophysiology, 45*, 60-69.

Horváth, J., Czigler, I., Sussman, E., & Winkler, I. (2001). Simultaneously active pre-attentive representations of local and global rules for sound sequences in the human brain. *Cogn. Brain Res., 12*, 131-144.

Howard, J., & Hudspeth, A. J. (1988). Compliance of the hair bundle associated with gating of mechanoelectrical transduction channels in the bullfrog's saccular hair cell. *Neuron, 1*, 189-199.

Hudspeth, A. J. (1989). How the ear's works work. *Nature, 341*(5), 397-404.

Hudspeth, A. J. (2000). Chapter 30: Hearing. In E. R. Kandel, J. H. Schwartz, & T. M. Jessell (Eds.), *Principles of Neural Science* (4 ed., pp. 590-613).

Imada, T., Hari, R., Loveless, N., McEvoy, L., & Sams, M. (1993). Determinants of the auditory mismatch response. *Electroencephalogr. Clin. Neurophysiol., 87*, 144-153.

Ivarsson, C., de Ribaupierre, Y., & de Ribaupierre, F. (1988). Influence of auditory localization cues on neuronal activity in the auditory thalamus of the cat. *J. Neurophysiol., 59*(2), 586-606.

Jacobsen, T., Horenkamp, T., & Schröger, E. (2003). Preattentive memory-based comparison of sound intensity. *Audiol. Neuro-otol., 8*(6), 338-346.

Jacobsen, T., & Schröger, E. (2001). Is there pre-attentive memory-based comparison of pitch? *Psychophysiology, 38*(4), 723-727.

Jacobsen, T., & Schröger, E. (2003). Measuring duration mismatch negativity. *Clin. Neurophysiol., 114*(6), 1133-1143.

Javitt, D. C., Grochowski, S., Shelley, A.-M., & Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. *Electroencephalogr. Clin. Neurophysiol., 108*, 143-153.

Jerger, J., Chmiel, R., Frost, J. D., & Coker, N. (1986). Effect of sleep on the auditory steady state potential. *Ear Hear., 7*(4), 240-245.

Kahneman, D., & Treisman, A. M. (1984). Changing views of attention and automaticity. In R. Parasuraman, & D. R. Davies (Eds.), *Varieties of Attention* (pp. 29-61). New York: Academic Press.

Kathmann, N., Frodl-Bauch, T., & Hegerl, U. (1999). Stability of the mismatch negativity under different stimulus and attention conditions. *Clin. Neurophysiol., 110*, 317-323.

Kauramäki, J., Jääskeläinen, I. P., & Sams, M. (2007). Selective attention increases both gain and feature selectivity of the human auditory cortex. *PLoS ONE, 2*(9), e909. doi:10.1371/journal.pone.0000909.

Kemp, D. T. (1978). Stimulated acoustic emissions from within the human auditory system. *J. Acoust. Soc. Am., 64*(5), 1386-1391.

Knight, R. T., Hillyard, S. A., Woods, D. L., & Neville, H. J. (1980). The effects of frontal and temporal-parietal lesions on the auditory evoked potential in man. *Electroencephalogr. Clin. Neurophysiol., 50* (1-2), 112-1124.

Koelsch, S., Heinke, W., Sammler, D., & Olthoff, D. (2006). Auditory processing during deep propofol sedation and recovery from unconsciousness. *Clin. Neurophysiol., 117*(8), 1746-1759.

Kramer, A. F., Trejo, L. J., & Humphrey, D. (1995). Assessment of mental workload with task-irrelevant auditory probes. *Biol. Psychol., 40*, 83-100.

Kraus, N., & McGee, T. J. (1995). The middle latency response generating system. In G. Karmos, V. Csépe, I. Czigler, M. Molnar, & J. Desmedt (Eds.), *Perspectives of Event-Related Potentials Research* (pp. 93-101). Amsterdam: Elsevier.

Lavie, N., Hirst, A., de Fockert, J.W., & Viding, E. (2004). Load theory of selective attention and cognitive control. *J. Exp. Psychol. Gen., 133*, 339-354.

Linden, R. D., Campbell, K. B., Hamel, G., & Picton, T. W. (1985). Human auditory steady state evoked potentials during sleep. *Ear Hear., 6*(3), 167-174.

Loewy, D. H., Campbell, K. B., & Bastien, C. (1996). The mismatch negativity to frequency deviant stimuli during natural sleep. *Electroencephalogr. Clin. Neurophysiol., 98*(6), 493-501.

Loewy, D. H., Campbell, K. B., de Lugt, D. R., Elton, M., & Kok, A. (2000). The mismatch negativity during natural sleep: intensity deviants. *Clin. Neurophysiol., 111*(5), 863-872.

Loomis, A. L., Harvey, E. N., & Hobart, G. A. (1938). Distribution of disturbance-patterns in the human encephalogram, with special reference to sleep. *J. Neurophysiol., 1*(5), 413-430.

Macdonald, M., Jamshidi, P., & Campbell, K. (2008). Infrequent increases in stimulus intensity may interrupt central executive functioning during Rapid Eye Movement sleep. *NeuroReport, 19*(3), 309-313.

Mäkelä, J. P., Hari, R., & Leinonen, L. (1988). Magnetic responses of the human auditory cortex to noise/square wave transitions. *Electroencaphalogr. Clin. Neurophysiol., 69*, 423-430.

Mäntysalo, S., & Näätänen, R. (1987). The duration of a neuronal trace of an auditory stimulus as indicated by event-related potentials. *Biol. Psychol., 24* (3), 183-195.

McCallum, W. C., Curry, S. H., Cooper, R., Pocock, P. V., & Papakostopoulos, D. (1983). Brain event-related potentials as indicators of early selective processes in auditory target localization. *Psychophysiology, 20*(1), 1-17.

Merzenich, M. M., Knight, P. L., & Roth, G. L. (1975). Representation of cochlea within primary auditory cortex in the cat. *J. Physiol., 38*(2), 231-249.

Middlebrooks, J. C., & Knudsen, E. I. (1984). A neural code for auditory space in the cat's superior colliculus. *J. Neurosci., 4*(10), 2621-2634.

Molholm, S., Gomes, H., Lobosco, J., Deacon, D., & Ritter, W. (2004). Feature versus gestalt representation of stimuli in the mismatch negativity system of 7- to 9-year-old children. *Psychophysiology, 41*, 385-393.

Møller, A. R. (1999). Neural mechaniss of BAEP. In C. Barber, G. Celesia, I. Hashimoto, & R. Kakigi (Eds.), *Functional Neuroscience: Evoked Potentials and Magnetic Fields* (pp. 27-35). Amsterdam: Elsevier.

Moray, N. (1959). Attention in dichotic listening: Affective cues and the influence of instructions. *Q. J. Exp. Psychol., 11*(1), 56-60.

Müller, B. W., Achenbach, C., Oades, R. D., Bender, S., & Schall, U. (2002). Modulation of mismatch negativity by stimulus deviance and modality of attention. *NeuroReport, 13*(10), 1317-1320.

Müller, D., & Schröger, E. (2007). Temporal grouping affects the automatic processing of deviant sounds. *Biol. Psychol., 74*, 358-364.

Mulders, W. H., & Robertson, D. (2000). Evidence for direct cortical innervation of medial olivocochlear neurones in rats. *Hear. Res., 144*, 65-72.

Muller-Gass, A., Macdonald, M., Schröger, E., Sculthorpe, L., & Campbell, K. (2007). Evidence for the auditory P3a reflecting an automatic process: Elicitation during highly-focused continuous visual attention. *Brain Res., 1170*, 71-78.

Muller-Gass, A., & Schröger, E. (2007). Perceptual and cognitive task difficulty has differential effects on auditory distraction. *Brain Res., 1136*, 169-177.

Muller-Gass, A., Stelmack, R. M., & Campbell, K. B. (2005). "...and were instructed to read a self-selected book while ignoring the auditory stimuli": The effects of task demands on the mismatch negativity. *Clin. Neurophysiol., 116* (9), 2142-2152.

Muller-Gass, A., Stelmack, R. M., & Campbell, K. B. (2006). The effect of visual task difficulty and attentional direction on the detection of acoustic change as indexed by the mismatch negativity. *Brain Res., 1078*, 112-130.

Näätänen, R. (1975). Selective attention and evoked potentials in humans: A critical review. *Biol. Psychol., 2*, 237-307.

Näätänen, R. (1982). Processing Negativity: An evoked-potential reflection of selective attention. *Psychol. Bull., 92*(3), 605-640.

Näätänen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behav. Brain Sci., 13*, 201-288.

Näätänen, R. (2007). The mismatch negativity: Where is the big fish? *J. Psychophysiol.*, *21*(3-4), 133-137.

Näätänen, R., & Alho, K. (1995). Mismatch negativity - A unique measure of sensory processing in audition. *Int. J. Neurosci., 80*, 317-337.

Näätänen, R., & Alho, K. (1997). Mismatch negativity - the measure for central sound representation accuracy. *Audiol. Neuro-otol., 2*(5), 341-353.

Näätänen, R., & Escera, C. (2000). Mismatch negativity (MMN): Clinical and other applications. *Audiol. Neuro-otol.*, *5*, 105-110.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol. (Amst.), 42*, 313-329.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1980). Brain potential correlates of voluntary and involuntary attention. *Prog. Brain Res., 54*, 343-348.

Näätänen, R., Sams, M., Järvilehto, T., & Soininen, K. (1982). Probability of deviant stimulus and event-related brain potentials. In *Psychophysiology 1980* (pp. 397-405). Amsterdam: VEB Gustav Fischer Verlag Jena and Elsevier Biomedical Press.

Näätänen, R., Jacobsen, T., & Winkler, I. (2005). Memory-based or afferent processes in mismatch negativity (MMN): A review of the evidence. *Psychophysiology*, *42*, 25-32.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K., & Sams, M. (1987). The mismatch negativity to intensity changes in an auditory stimulus sequence. *Electroencephalogr. Clin. Neurophysiol. Suppl. 40,* 125-131.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K., & Sams, M. (1989). Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? *Neurosci. Lett., 98*, 217-221.

Näätänen, R., Paavilainen, P., & Reinikainen, K. (1989). Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? *Neurosci. Lett., 107*, 347-352.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clin. Neurophysiol., 118*, 2544-2590.

Näätänen, R., Paavilainen, P., Alho, K., Reinikainen, K., & Sams, M. (1987). Interstimulus interval and mismatch negativity. In C. Barber, & T. Blum (Eds.), *Evoked Potentials III* (pp. 392-397). London: Butterworths.

Näätänen, R., Paavilainen, P., Tiitinen, H., Jiang, D., & Alho, K. (1993). Attention and mismatch negativity. *Psychophysiology, 30*, 436-450.

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

Näätänen, R., Sams, M., Järvilehto, T., & Soininen, K. (1982). Probability of deviant stimulus and event-related brain potentials. In *Psychophysiology 1980* (pp. 397-405). Amsterdam: VEB Gustav Fischer Verlag Jena and Elsevier Biomedical Press.

Näätänen, R., Simpson, M., & Loveless, N. E. (1982). Stimulus deviance and evoked potentials. *Biol. Psychol., 14*, 53-98.

Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., & Winkler,I., (2001). "Primitive intelligence" in the auditory cortex. *Trends Neurosci. 24*, 283-288.

Näätänen, R., & Winkler, I. (1999). The concept of auditory stimulus representation in cognitive neuroscience. *Psychol. Bull., 125*(6), 826-859.

Nashida, T., Yabe, H., Sato, Y., Sutoh, T., Shinozaki, N., & Kaneko, S. (2000). Automatic auditory information processing in sleep. *Sleep, 23*(6), 821-828.

Neely, S. T., & Kim, D. O. (1983). An active cochlear model showing sharp tuning and high sensitivity. *Hear. Res., 9*, 123-130.

Neisser, U. (1967). *Cognitive psychology.* New York: Appleton-Century-Crofts.

Nielsen-Bohlman, L., Knight, R. T., Woods, D. L., & Woodward, K. (1991). Differential auditory processing continues during sleep. *Electroencephalogr. Clin. Neurophysiol., 79*(4), 281-290.

Nittono, H., Momose, D., & Hori, T. (2001). The vanishing point of the mismatch negativity at sleep onset. *Clin. Neurophysiol., 112*(5), 732-739.

Nordby, H., Roth, W. T., & Pfefferbaum, A. (1988a). Event-related potentials to time-deviant and pitch-deviant tones. *Psychophysiology, 25*, 249-261.

Nordby, H., Roth, W. T., & Pfefferbaum, A. (1988b). Event-related potentials to breaks in sequences of alternating pitches or interstimulus intervals. *Psychophysiology, 25*, 262-268.

Norman, D. A. (1968). Toward a theory of memory and attention. *Psychol. Rev., 75*(6), 522-536.

Novak, G. P., Ritter, W., Vaughan, H. G., & Wiznitzer, M. L. (1990). Differentiation of event-related potentials in an auditory discrimination task. *Electroencephalogr. Clin. Neurophysiol., 75*(4), 255-275.

Ogilvie, R. D., Simons, I. A., Kuderian, R. H., MacDonald, T., & Rustenburg, J. (1991). Behavioral, event-related potential, and EEG/FFT changes at sleep onset. *Psychophysiology, 28*(1), 54-64.

Oksama, L., & Hyönä, J. (2004). Is multiple object tracking carried out automatically by an early vision mechanism independent of higher-order cognition? An individual difference approach. *Vis. Cogn., 11*, 631-671.

Osterhammel, P. A., Shallop, J. K., & Terkildsen, K. (1985). The effect of sleep on the auditory brainstem response (ABR) and the middle latency response (MLR). *Scand. Audiol., 14*(1), 47-50.

Otten, L. J., Alain, C., & Picton, T. W. (2000). Effects of visual attentional load on auditory processing. *NeuroReport, 11*(4), 875-880.

Ozaki, I., Jin, C. Y., Suzuki, Y., Baba, M., Matsunaga, M., & Hashimoto, I. (2004). Rapid changes of tonotopic maps in the human auditory cortex during pitch discrimination. *Clin. Neurophysiol., 115*, 1592-1604.

Paavilainen, P., Cammann, R., Alho, K., Reinikainen, K., Sams, M., & Näätänen, R. (1987). Event-related potentials to pitch change in an auditory stimulus sequence during sleep. *Electroencephalogr. Clin. Neurophysiol. (Suppl.), 40*, 246-255.

Paavilainen, P., Degerman, A., Takegata, R., & Winkler, I. (2003). Spectral and temporal stimulus characteristics in the processing of abstract auditory features. *NeuroReport, 14*, 715-718.

Paavilainen, P., Jaramillo, M., Näätänen, R., & Winkler, I. (1999). Neuronal populations in the human brain extracting invariant relationships from acoustic variance. *Neurosci. Lett., 265*, 179-182.

Paavilainen, P., Karlsson, M.L., Reinikainen, K., & Näätänen, R. (1989). Mismatch negativity to change in spatial location of an auditory stimulus. *Electroencephalogr. Clin. Neurophysiol., 73*, 129-141.

Paavilainen, P., Tiitinen, H., Alho, K., & Näätänen, R. (1993). Mismatch negativity to slight pitch changes outside strong attentional focus. *Biol. Psychol., 37*, 23-41.

Palmer, A. R., Rees, A., & Caird, D. (1992). Binaural masking and sensitivity to interaural delay in the inferior colliculus. *Philos. Trans. R. Soc. Lond. B Biol. Sci., 336*, 415-422.

Pantev, C., Hoke, M., Lehnertz, K., & Lütkenhöner, B. (1989). Neuromagnetic evidence of an ampliotopic organization of the human auditory cortex. *Electroencephalogr. Clin. Neurophysiol., 72*, 225-231.

Pantev, C., Hoke, M., Lütkenhöner, B., Anogianakis, G., & Wittkowski, W. (1988). Tonotopic organization of the human auditory cortex revealed by transient auditory evoked magnetic fields. *Electroencephalogr. Clin. Neurophysiol., 69*, 160-170.

Parasuraman, R., Richer, F., & Beatty, J. (1982). Detection and recognition: Concurrent processes in perception. *Percept. Psychophys., 31* (1), 1-12.

Pedemonte, M., Peña, J. L., & Velluti, R. A. (1996). Firing of inferior colliculus auditory neurons is phase-locked to the hippocampus theta rhythm during paradoxical sleep and waking. *Exp. Brain Res., 112*, 41-46.

Petkov, C. I., Kang, X., Alho, K., Bertrand, O., Yund, E. W., & Woods, D. L. (2004). Attentional modulation of human auditory cortex. *Nat. Neurosci.*, *7*(6), 658-663.

Picton, T. W., Alain, C., Otten, L., Ritter, W., & Achim, A. (2000). Mismatch negativity: Different water in the same river. *Audiol. Neuro-otol.*, *5*(3-4), 111-139.

Picton, T. W., & Hillyard, S. A. (1974). Human auditory evoked potentials. II: Effects of attention. *Electroencephalogr. Clin. Neurophysiol., 36*, 191-199.

Picton, T. W., Hillyard, S. A., Krausz, H. I., & Galambos, R. (1974). Human auditory evoked potentials. I: Evaluation of components. *Electroencephalogr. Clin. Neurophysiol., 36*, 179-190.

Picton, T. W., Stapells, D. R., & Campbell, K. B. (1981). Auditory evoked potentials from the human cochlea and brainstem. *J. Otolaryngol. (Suppl.), 9*, 1-41.

Posner, M. I., & Snyder, C. R. (1975a). Attention and cognitive control. In R. L. Solso (Ed.), *Information Processing and Cognition: The Loyola Symposium* (pp. 55-85). Hillsdale, NJ: Erlbaum.

Posner, M. I., & Snyder, C. R. (1975b). Facilitation and inhibition in the processing of signals. In P. M. Rabitt, & S. Dornic (Eds.), *Attention and Performance V* (pp. 669-698). New York: Academic Press.

Pylyshyn, Z.W., & Storm, R.W. (1988). Tracking multiple independent targets: evidence for a parallel tracking mechanism. *Spat. Vis., 3*, 179-197.

Rechtschaffen, A., & Kales, A. (1968). A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects, BIS/BRI, UCLA, Los Angeles.

Regan, D. (1982). Comparison of transient and steady-state methods. *Ann. N.Y. Acad. Sci., 388*, 45-71.

Restuccia, D., Della Marca, G., Marra, C., Rubino, M., & Valeriani, M. (2005). Attentional load of the primary task infuences the frontal but not the temporal generators of mismatch negativity. *Cogn. Brain Res., 25*, 891-899.

Rhode, W. S. (1991). Physiological-morphological properties of the cochlear nucleus. In R. A. Altschuler, R. P. Bobbin, B. M. Clopton, & D. W. Hoffman (Eds.), *Neurobiology of Hearing: The Central Auditory System* (pp. 47-77). New York: Raven Press.

Rinne, T., Alho, K., Ilmoniemi, R.J., Virtanen, J., & Näätänen, R. (2000). Separate time behaviors of the temporal and frontal mismatch negativity sources. *NeuroImage, 12*, 14-19.

Ritter, W., Vaughan, H. G., & Costa, L. D. (1968). Orienting and habituation to auditory stimuli: A study of short-term changes in averaged evoked responses. *Electroencephalogr. Clin. Neurophysiol., 25*, 550-556.

Rivier, F., & Clarke, S. (1997). Cytochrome oxidase, acetylcholinesterase, and NADPH-Diaphorase staining in human supratemporal and insular cortex: Evidence for multiple auditory areas. *NeuroImage, 6*, 288-304.

Robertson, D. (1984). Horseradish peroxidase injection of physiologically characterized afferent and efferent neurones in the guinea pig spiral ganglion. *Hear. Res., 15*, 113-121.

Ruby, P., Caclin, A., Boulet, S., Delpuech, C., & Morlet, D. (2008). Odd sound processing in the sleeping brain. *J. Cogn. Neurosci., 20*(2), 296-311.

Ryan, A., Dallos, P., & McGee, T. (1979). Psychophysical tuning curves and auditory thresholds after hair cell damage in the chinchilla. *J. Acoust. Soc. Am., 66*(2), 370-378.

Saarinen, J., Paavilainen, P., Schröger, E., Tervaniemi, M., & Näätänen, R. (1992). Representation of abstract attributes of auditory stimuli in the human brain. *NeuroReport, 3*(12), 1149-1151.

Sabri, M., & Campbell, K. B. (2001). Effects of sequential and temporal probability of deviant occurrence on mismatch negativity. *Cogn. Brain Res., 12*, 171-180.

Sabri, M., & Campbell, K. B. (2002). The effects of digital filtering on mismatch negativity in wakefulness and sow-wave sleep. *J. Sleep Res., 11*(2), 123-127.

Sabri, M., & Campbell, K. B. (2005). Is the failure to detect stimulus deviance during sleep due to a rapid fading of sensory memory or a degradation of stimulus encoding? *J. Sleep Res., 14*(2), 113-122.

Sabri, M., De Lugt, D.R., & Campbell, K.B. (2000). The mismatch negativity to frequency deviants during the transition from wakefulness to sleep. *Can. J. Exp. Psychol., 54*, 230-242.

Sabri, M., Labelle, S., Gosselin, A., & Campbell, K.B. (2003). Effects of sleep onset on the mismatch negativity (MMN) to frequency deviants using a rapid rate of presentation. *Brain Res. Cogn. Brain Res., 17*, 164-176.

Sahley, T. L., Nodar, R. H., & Musiek, F. E. (1997). *Efferent Auditory System.* San Diego, CA: Singular Publishing.

Salisbury, D., & Squires, N. K. (1993). Response properties of long-latency event-related potentials evoked during NREM sleep. *J. Sleep Res., 2*(4), 232-240.

Sallinen, M., Kaartinen, J., & Lyytinen, H. (1994). Is the appearance of mismatch negativity during stage 2 sleep related to the elicitation of K-complex? *Electroencephalogr. Clin. Neurophysiol., 91*, 140–148.

Sallinen, M., Kaartinen, J., & Lyytinen, H. (1997). Precursors of the evoked K-complex in event-related brain potentials in stage 2 sleep. *Electroencephalogr. Clin. Neurophysiol., 102*(4), 363-373.

Sallinen, M., & Lyytinen, H. (1997). Mismatch negativity during objective and subjective sleepiness. *Psychophysiology, 34*, 694-702.

Sams, M., Alho, K., & Näätänen, R. (1983). Sequential effects on the ERP in discriminating two stimuli. *Biol. Psychol., 17*, 41-58.

Sams, M., Alho, K., & Näätänen, R. (1984). Short-term habituation and dishabituation of the mismatch negativity ERP. *Psychophysiology, 21*(4), 434-441.

Sams, M., Hämäläinen, M., Antervo, A., Kaukoranta, E., Reinikainen, K., & Hari, R. (1985). Cerebral neuromagnetic responses evoked by short auditory stimuli. *Electroencephalogr. Clin. Neurophysiol., 61*, 254-266.

Sams, M., Hari, R., Rif, J., & Knuutila, J. (1993). The human auditory sensory memory trace persists about 10 sec: Neuromagnetic evidence. *J. Cogn. Neurosci., 5*(3), 363-370.

Sams, M., Paavilainen, P., Alho, K., & Näätänen, R. (1985). Auditory frequency discrimination and event-related potentials. *Electroencephalogr. Clin. Neurophysiol., 62*, 437-448.

Sato, Y., Yabe, H., Hiruma, T., Sutoh, T., Shinozaki, N., Nashida, T., et al. (2000). The effect of deviant stimulus probability on the human mismatch process. *NeuroReport, 11*(17), 3703-3708.

Sato, Y., Yabe, H., Todd, J., Michie, P., Shinozaki, N., Sutoh, T., et al. (2003). Impairment of a frontal attention-switch mechanism in schizophrenic patients. *Biol. Psychol., 62*(1), 49-63.

Scharf, B., & Houtsma, A. J. (1986). Audition. II. Loudness, pitch, localization, aural distortion, pathology. In K. R. Boff, L. Kaufman, & J. P. Thomas (Eds.), *Handbook of Perception and Human Performance. Vol. I. Sensory Processes and Perception* (pp. 15-60). New York: Wiley.

Scherg, M., & von Cramon, D. (1986). Evoked dipole source potentials of the human auditory cortex. *Electroencephalogr. Clin. Neurophysiol., 65*, 344-360.

Schneider, W., & Shiffrin, R. M. (1977). Controlled and automatic human information processing: I. Detection, search, and attention. *Psychol. Rev., 84*(1), 1-66.

Schröger, E. (2007). Mismatch negativity, a microphone into auditory memory. *J. Psychophysiol. 21*(3-4), 138-146.

Schröger, E., & Wolff, C. (1996). Mismatch response of the human brain to changes in sound location. *NeuroReport, 7*, 3005-3008.

Schröger, E., & Wolff, C. (1998). Behavioral and electrophysiological effects of task-irrelevant sound change: a new distraction paradigm. *Brain Res. Cogn Brain Res., 7*, 71-87.

Schwent, V. L., & Hillyard, S. A. (1975). Evoked potential correlates of selective attention with multi-channel auditory inputs. *Electroencephalogr. Clin. Neurophysiol., 38*, 131-138.

Sculthorpe, L.D., Collin, C.A., & Campbell, K.B. (2008). The influence of strongly focused visual attention on the detection of change in an auditory pattern. *Brain Res., 1234*, 78-86.

Sculthorpe, L. D., Ouellet, D. R., & Campbell, K. B. (2009). MMN elicitation during natural sleep to violations of an auditory pattern. *Brain Res., 1290*, 52-62.

Sculthorpe, L. D., Stelmack, R. M., & Campbell, K. B. (2009). Mental ability and the effect of pattern violation discrimination on P300 and mismatch negativity. *Intelligence, 37*, 405-411.

Shalgi, S., & Deouell, L. Y. (2007). Direct evidence for differential roles of temporal and frontal components of auditory change detection. *Neuropsychologia, 45*(8), 1878-1888.

Shelley, A.-M., Silipo, G., & Javitt, D. C. (1999). Diminished responsiveness of ERPs in schizophrenic subjects to changes in auditory stimulation parameters: Implications for theories of cortical dysfunction. *Schizophr. Res., 37, 65-79.*

Sinkkonen, J., Kaski, S., Huotilainen, M., Ilmoniemi, R. J., Näätänen, R., & Kaila, K. (1996). Optimal resource allocation for novelty detection in a human auditory memory. *NeuroReport, 7*(15-17), 2479-2482.

Sonnadara, R. R., Alain, C., & Trainor, L. J. (2006). Effects of spatial separation and stimulus probability on the event-related potentials elicited by occasional changes in sound location. *Brain Res., 1071*, 175-185.

Spangler, K. M., & Warr, W. B. (1991). The descending auditory system. In R. A. Altschuler, R. P. Bobbin, B. M. Clopton, & D. W. Hoffman (Eds.), *Neurobiology of Hearing: The Central Auditory System* (pp. 27-45). New York: Raven Press.

Spitzer, H., Desimone, R., & Moran, J. (1988). Increased attention enhances both behavioral and neuronal performance. *Science, 240*(4850), 338-340.

Spoor, A., Timer, F., & Odenthal, D. W. (1969). The evoked auditory response (ear) to intensity modulated and frequency modulated tones and tone bursts. *International Audiology, 8*, 410-415.

Squires, N. K., Squires, K. C., & Hillyard, S. A. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalogr. Clin. Neurophysiol., 38*, 387-401.

Sussman, E. (2007). A new view on the MMN and attention debate. *J. Psychophysiol., 21*, 164-175.

Sussman, E., & Gumenyuk, V. (2005). Organization of sequential sounds in auditory memory. *NeuroReport, 16*, 1519-1523.

Sussman, E., Ritter, W., & Vaughan, H. G. (1998). Predictability of stimulus deviance and the mismatch negativity. *NeuroReport, 9*(18), 4167-4170.

Sussman, E., Winkler, I., & Wang, W. (2003). MMN and attention: Competition for deviance detection. *Psychophysiology, 40*, 430-435.

Szymanski, M. D., Yund, E. W., & Woods, D. L. (1999). Phonemes, intensity and attention: Differential effects on the mismatch negativity (MMN). *J. Acoust. Soc. Am., 106*(6), 3492-3505.

Takegata, R., Roggia, S. M., & Winkler, I. (2005). Effects of temporal grouping on the memory representation of inter-tone relationships. *Biol. Psychol., 68*, 41-60.

Tervaniemi, J., Maury, S., & Näätänen, R. (1994). Neural representations of abstract stimulus features in the human brain as reflected by the mismatch negativity. *NeuroReport, 5*(7), 844-846.

Tervaniemi, M., Rytkönen, M., Schröger, E., Ilmoniemi, R. J., & Näätänen, R. (2001). Superior formation of cortical memory traces for melodic patterns in musicians. *Learn. Mem., 8*(5), 295-300.

Tiitinen, H., May, P., Reinikainen, K., & Näätänen, R. (1994). Attentive novelty detection in humans is governed by pre-attentive sensory memory. *Nature, 372*, 90-92.

Tonndorf, J. (1960). Shearing motion in scala media of cochlear models. *J. Acoust. Soc. Am., 32*(2), 238-244.

Treisman, A. M. (1964). Verbal cues, language, and meaning in selective attention. *Am. J. Psychol., 77*, 206-219.

Trejo, L.J., Ryan-Jones, D.L., & Kramer, A.F. (1995). Attentional modulation of the mismatch negativity elicited by frequency differences between binaurally presented tone bursts. *Psychophysiology, 32*, 319-328.

Vaughan, H. G., & Arezzo, J. C. (1988). The neural basis of event-related potentials. In T. W. Picton (Ed.), *Human Event-Related Potentials (Vol. 3)* (pp. 45-96). Amsterdam: Elsevier.

Vaughan, H. G., & Ritter, W. (1970). The sources of auditory evoked responses recorded from the human scalp. *Electroencephalogr. Clin. Neurophysiol., 28*, 360-367.

Velluti, R. A. (2008). *The Auditory System in Sleep.* Amsterdam: Elsevier.

von Békésy, G. (1970). Travelling waves as frequency analysers in the cochlea. *Nature, 225*, 1207-1209.

Wallace, M. N., Johnston, P. W., & Palmer, A. R. (2002). Histochemical identification of cortical areas in the auditory region of the human brain. *Exp. Brain Res., 143*, 499-508.

Watkins, M. J., & Todres, A. K. (1980). Suffix effects manifext and concealed: Further evidence for a 20-second echo. *Journal of Verbal Learning and Verbal Behavior, 19*, 46-53.

Wijnen, V. J., van Boxtel, G. J., Eilander, H. J., & de Gelder, B. (2007). Mismatch negativity predicts recovery from the vegetative state. *Clin. Neurophysiol., 118*(3), 597-605.

Winer, B.J. (1971). Statistical Principles in Experimental Design, McGraw-Hill, New York.

Winer, J. A. (2006). Decoding the auditory corticofugal systems. *Hear. Res., 212*, 1-8.

Winer, J. A., Diehl, J. J., & Larue, D. T. (2001). Projections of auditory cortex to the medial geniculate body of the cat. *J. Comp. Neurol., 430*, 27-55.

Winer, J. A., Larue, D. T., Diehl, J. J., & Hefti, B. J. (1998). Auditory cortical projections to the cat inferior colliculus. *J. Comp. Neurol., 400*, 147-174.

Winkler, I. (2007). Interpreting the mismatch negativity. *J. Psychophysiol., 21*, 147-163.

Winkler, I., Cowan, N., Csépe, V., Czigler, I., & Näätänen, R. (1996). Interactions between transient and long-term auditory memory as reflected by the mismatch negativity. *J. Cogn. Psychol.*, *8*(5), 403-415.

Winkler, I., Karmos, G., & Näätänen, R. (1996). Adaptive modeling of the unattended acoustic environment reflected in mismatch negativity event-related potential. *Brain Res.*, *742*, 239-252.

Winkler, I., Korzyukov, O., Gumenyuk, V., Cowan, N., Linkenkaer-Hansen, K., Ilmoniemi, R. J., et al. (2002). Temporary and longer term retention of acoustic information. *Psychophysiology, 39*, 530-534.

Winkler, I., Lehtokoski, A., Alku, P., Vainio, M., Czigler, I., Csépe, V., et al., (1999). Pre-attentive detection of vowel contrasts utilizes both phonetic and auditory memory representations. *Brain Res. Cogn Brain Res., 7*, 357-369.

Winkler, I., & Schröger, E., (1995). Neural representation for the temporal structure of sound patterns. *NeuroReport, 6*, 690-694.

Winter, O., Kok, A., Kenemans, J. L., & Elton, M. (1995). Auditory event-related potentials to deviant stimuli during drowsiness and stage 2 sleep. *Electroencephalogr. Clin. Neurophysiol., 96*(5), 398-412.

Woestenburg, J.C., Verbaten, M.N., & Slangen, J.L. (1983). The removal of the eye-movement artifact from the EEG by regression analysis in the frequency domain. *Biol. Psychol., 16*, 127-147.

Woldorff, M. G., Hackley, S. A., & Hillyard, S. A. (1991). The effects of channel-selective attention on the mismatch negativity wave elicited by deviant tones. *Psychophysiology, 28*(1), 30-42.

Woldorff, M., Hansen, J. C., & Hillyard, S. A. (1987). Evidence for effects of selective attention in the mid-latency range of the human auditory event-related potential. In R. Johnson Jr., J. W. Rohrbaugh, & R. Parasuraman (Eds.), *Current Trends in Event-Related Potential Research (EEG Suppl. 40)* (pp. 146-154). Amsterdam: Elsevier.

Woldorff, M. G., & Hillyard, S. A. (1991). Modulation of early auditory processing during selective listening to rapidly presented tones. *Electroencephalogr. Clin. Neurophysiol., 79*, 170-191.

Woldorff, M. G., Hillyard, S. A., Gallen, C. C., Hampson, S. R., & Bloom, F. E. (1998). Magnetoencephalographic recordings demonstrate attentional modulation of mismatch-related neural activity in human auditory cortex. *Psychophysiology, 35*, 283-292.

Wolpaw, J. R., & Penry, J. K. (1975). A temporal component of the auditory evoked response. *Electroencephalogr. Clin. Neurophysiol., 39*, 609-620.

Wong, D., & Kelly, J. P. (1981). Differentially projecting cells in individual layers of the auditory cortex: A double-labeling study. *Brain Res., 230*, 362-366.

Woods, D. L., Alho, K., & Algazi, A. (1992). Intermodal selective attention. I. Effects on event-related potentials to lateralized auditory and visual stimuli. *Electroencephalogr. Clin. Neurophysiol., 82*, 341-355.

Woods, D. L., & Hillyard, S. A. (1978). Attention at the cocktail party: Brainstem evoked responses reveal no peripheral gating. In D. A. Otto (Ed.), *Multidisciplinary Perspectives in Event-Related Brain Potential Research* (pp. 230-233). Washington, DC: U.S. Government Printing Office.

Yucel, G., Petty, C., McCarthy, G., & Belger, A. (2005). Graded visual attention modulates brain responses evoked by task-irrelevant auditory pitch changes. *J. Cogn. Neurosci., 17*(2), 1819-1828.

Zachau, S., Rinker, T., Körner, B., Kohls, G., Maas, V., Hennighausen, K., et al. (2005). Extracting rules: early and late mismatch negativity to tone patterns. *NeuroReport, 16*, 2015-19.

Zhang, P., Chen, X., Yuan, P., Zhang, D., & He, S. (2006). The effect of visuospatial attentional load on the processing of irrelevant acoustic distractors. *NeuroImage, 33*, 715-724.