

Potential Contamination Effects of Neuronal Refractoriness on the Speech-evoked Mismatch Negativity Response

Jerry L. Cranford*

Letitia J. Walker*

Andrew Stuart*

Saravanan Elangovan*

David Pravica†

Abstract

The mismatch negativity response (MMN) is an event-related potential that is believed to reflect the automatic (possibly preconscious) neural processing of changes in ongoing environmental sounds. The MMN involves a negative voltage shift of baseline electroencephalographic (EEG) activity in the approximate latency window of the N1 and P2 cortical potentials in response to new or novel sounds. The most commonly used laboratory tests for extracting the MMN from EEG activity all involve oddball stimulus presentation procedures in which the interstimulus intervals (ISIs) of the frequently occurring standard sounds are shorter in length than that of the infrequently occurring deviant sounds. This presents the possibility that the MMN response could be affected by neuronal refractory or recovery events. The present study tested 12 young females, using the syllabic events /da/ and /ga/ as standard and deviant stimuli, and found evidence that, with certain experimental protocols, ISI-dependent neural refractory effects can affect the morphology of the MMN, possibly resulting in misinterpretation of the underlying neural bases of the response.

Key Words: Auditory event-related potentials, auditory evoked potentials, mismatch negativity, speech

Abbreviations: ANOVA = Analysis of variance, EEG = electroencephalographic, LAEP = late auditory evoked potentials, MMN = mismatch negativity, SOA = stimulus onset asynchrony

Sumario: La respuesta negatividad desigual (Mismatch negativity: MMN) es un potencial relacionado con un evento que se cree refleja el procesamiento neural automático (posiblemente pre-conciente) de los cambios en sonidos ambientales continuos. La MMN involucra un cambio negativo de voltaje de la actividad electroencefalográfica (EEG) basal, en la ventana aproximada de latencia de los potenciales corticales N1 y P2, en respuesta a sonidos nuevos o llamativos. Todas las pruebas de laboratorio más comúnmente utilizadas para extraer la MMN de la actividad EEG involucran procedimientos de presentación del estímulo, en los que el intervalo inter-estímulo (ISI) del sonido estándar que ocurre en forma frecuente es más corto en duración que aquél del sonido diferente que ocurre con menor frecuencia. Esto establece la posibilidad de que la respuesta MMN pudiera ser afectada por eventos refractarios o de recuperación neuronal. El presente estudio evaluó 12 mujeres afectadas, utilizando los eventos silábicos /da/ y /ga/, como estímulo estándar y disímil, y se encontró evidencia de que con ciertos protocolos experimentales, los efectos refractarios neurales dependientes del ISI pueden afectar la morfología

* Department of Communication Sciences and Disorders, East Carolina University, Greenville, North Carolina

† Department of Mathematics, East Carolina University, Greenville, North Carolina

Address correspondence to: Jerry L. Cranford, Ph.D., Dept. of Communication Disorders, School of Allied Health Professions, LSU Health Science Center, 1900 Gravier Street, New Orleans, LA 70112. Phone: (504) 568-4345. Email: jcranf@lsuhsc.edu

de la MMN, posiblemente conduciendo a errores de interpretación en cuanto a las bases neurales subyacentes de la respuesta.

Palabras Clave: Potenciales auditivos relacionados con el evento, potenciales evocados auditivos, negatividad desigual, habla.

Abreviaturas: ANOVA = Análisis de variancia, EEG = electroencefalografía, LAEP = potenciales evocados auditivos tardíos, MMN = negatividad desigual, SOA = asincronía en el inicio del estímulo.

The individual neural components of the late auditory evoked potential (LAEP) can be categorized into those that depend on the physical nature of the eliciting stimulus (exogenous) and those that depend on the psychological or cognitive processing (endogenous) of stimulus information by the listener. Whereas exogenous potentials provide useful information regarding the physiologic integrity of peripheral and central auditory pathways, endogenous potentials provide important clues to the nature of higher mental functions. Beginning with the discovery (Sutton, Braren, Zubin, & John, 1965) of the P300 event-related potential (ERP), cognitive neuroscientists have been searching for additional forms of electrophysiologic correlates of higher level attentional or memory processes in the human brain. In 1973, Hillyard and his colleagues (Hillyard, Hink, Schwent, & Picton, 1973) developed a special ERP paradigm that provided the first controlled evidence of electrical signs of active attentional processing in the brain. In the summer of 1975, Naatanen and his colleagues (Naatanen, Gaillard, & Mantysalo, 1978) discovered evidence of what appeared to be a passive or preconscious form of attentional ERP. This has been labeled the "mismatch negativity" (MMN). The MMN involves a negative voltage shift of baseline EEG activity in response to any discriminable change in a repetitive sound. It frequently overlaps the latency window of the N1 and P2 components of the LAEP. The MMN appears to be present at birth (Alho, Sainio, Sajaniemi, Reinikainen, & Naatanen, 1990) and does not require attention or a behavioral response from the participant (Naatanen & Teder, 1991; Novak,

Ritter, & Vaughan, 1992). It has been found to occur in sleeping adults (Nielsen-Bohlman, Knight, Woods, & Woodward, 1988) and in some comatose patients (Kane, Curry, Butler, & Cummins, 1993).

Since the MMN involves a negative voltage shift of EEG activity in response to a rare stimulus event (i.e., changes in ongoing background sounds), two basic laboratory procedures have been developed for extracting the response from EEG activity. The first test paradigm involves presentation of an oddball sequence of repetitive sounds in which "deviant" sounds are randomly interspersed among "standard" sounds, with the former sounds differing in some specific way (e.g., frequency, intensity) from the latter. The standard sounds are typically presented more frequently than the deviant sounds. A difference wave is then computed in which the waveform elicited by the standard stimulus is subtracted from the response to the deviant stimulus.

The second test paradigm involves recording the response to a train of deviant stimuli presented alone and subtracting this response from the response to the same deviant stimulus when it is presented as part of the oddball sequence. Since, with both MMN extraction procedures, the deviant and standard stimuli are presented with different inter-stimulus intervals (ISIs), this presents the possibility of a technical flaw related to neuronal refractoriness or recovery. It is well known (Nelson & Lassman, 1968, 1973, 1977; Budd, Barry, Gordon, Rennie, & Michie, 1998; Butler, 1973) that increasing the ISI between adjacent stimuli in a stimulus train will result in increased amplitudes of the exogenous components of the LAEP (e.g., N1, P2). Thus, if the deviant and standard stimuli, because of their physical differences, triggered

different populations of neural units, any increased negativity seen in the MMN difference wave might be the result of the deviant stimuli having longer ISIs than the standard stimuli.

In a recently completed study, the present authors (Walker, Carpenter, Downs, Cranford, Stuart, & Pravica, 2001) recorded MMNs to tonal stimuli in a group of young adults and obtained evidence that, with some experimental protocols, ISI-dependent amplitude changes in N1 and/or P2 can alter the morphology of the difference waves that could result in misinterpretation of the nature of the underlying MMN generators. The purpose of the present study was to investigate, using a similar experimental design, whether evidence of neuronal refractory artifacts might be found when the MMN response is elicited by more complex speech stimuli rather than pure tones.

METHOD

Participants

Twelve young adult female listeners were tested. They ranged in age from 20 years, 4 months to 27 years, 5 months ($M = 22$ years, 0 months) and had pure tone averages of 20 dB HL or better at octave frequencies from 500 to 4000 Hz, with interaural differences less than 10 dB HL at all frequencies. Tympanometry screening revealed normal middle ear function (ASHA, 1990). All participants were right handed with negative histories of neurologic or otologic problems.

Apparatus and Procedures

Stimuli. The stimuli consisted of two syllabic events, “da” and “ga” imported from the Dichotic Nonsense Syllables subtest of the Speech Recognition and Identification Materials Disc 1.1 (VA Medical Center, Long Beach, CA). The recorded signals were cropped to set the trigger point at the beginning of aspiration of the consonant. Durations were set at 300 ms, the ending point of phonation of the vowel. Stimuli were presented to the right ear at 65 dBpSPL with insert receivers (Etymotic ER-3A).

Test Procedures. Since the discovery of the MMN, three different laboratory paradigms have been used to extract the MMN response from background EEG activity. The present participants received a series of test runs that allowed extracting a MMN response with each of the three experimental procedures. Table 1 shows the stimulus format for the present project. The order in which the five types of test runs were administered to individual participants was counterbalanced using Latin Square logic. The time required to administer all five test runs to each individual participant was approximately 1.5 hours.

The first MMN extraction procedure (which, for purposes of the present project, we have labeled the “Deviant-in-Oddball” or “DO” method) involved a traditional oddball paradigm (Squires & Hecox, 1983). The deviant /ga/ stimuli, with a 15% probability of occurrence, were randomly intermixed among standard /da/ stimuli which had a probability of occurrence of 85%. To estimate the MMN response, a difference wave was

Table 1. Shows the five types of stimulus test runs administered to the participants, plus which test runs were used in deriving MMN responses with each of the three extraction methods.

Test Run	Standard	Deviant	ISI (msec)	# Stimuli	MMN Method
1	/da/	/ga/	250	1400	FF/DO/DA
2	/ga/	/da/	250	1400	FF
3	-	/ga/	250	210	DA
4	-	/ga/	800	210	DA
5	-	/ga/	1900	210	DA

Note: DO = Deviant-in-Oddball MMN extraction procedure; DA = Deviant-Alone procedure; and FF = Flip-flop extraction method.

calculated in which the waveform elicited by the standard stimuli was subtracted from the waveform elicited by the deviant stimuli. Test run #1 was used for this comparison. Each oddball run involved the presentation of 1190 standard and 210 deviant stimuli. Stimuli were presented in a pseudorandom sequence with an Interstimulus Interval (ISI) of 250 ms. At least three standard stimuli preceded the occurrence of the first deviant stimulus. In each test run, 20 standard stimuli preceded the occurrence of the first deviant stimulus. These 20 stimuli were not included in the response average. Responses to standard stimuli immediately following deviant stimuli were also excluded from response averages.

The second MMN extraction procedure (i.e., the "Deviant-Alone" or "DA" method) involved presentation of oddball sequences containing standards and deviants plus presentation of separate test runs involving deviant stimuli alone. Waveforms recorded to the deviant stimuli in test run #1 were compared to those from runs 3, 4, and 5. ISIs of 250, 800, and 1900 ms were used in these deviant-alone test runs. The choice of specific ISI values for these deviant-alone test runs was somewhat arbitrary. We wished to select a range of ISIs that would clearly demonstrate neural refractory effects, if present. An ISI of 250 ms was used during all administrations of test runs 1 and 2. The average ISI between consecutive deviant stimuli on these oddball runs approximated 3100 ms. Difference waves were then calculated in which the waveform elicited by each deviant-alone condition was subtracted from that recorded with the deviants when they were presented as part of the oddball sequence.

The third MMN extraction procedure (i.e., the "Flip-Flop" or "FF" method), which is a variation of the DO method, involved administering two oddball test runs in which the speech stimulus that served as the deviant in one test run was made to serve as the standard stimulus in the other test run. Test runs 1 and 2 were used in this comparison. To estimate the MMN response, a difference wave was calculated in which the waveform elicited by the stimulus when it was the standard was subtracted from the same stimulus when it served as the deviant.

Electrophysiological recording and data analysis procedures. Participants were seated in a reclining chair in an electrically -shielded and sound-treated

chamber and instructed to relax and read a self-selected book. Electroencephalographic (EEG) activity was recorded from a vertex electrode site (i.e., Cz re. The 10-20 system) referenced to the nasion. Vertical eye movements were recorded from electrodes placed above and below the left eye. Electrode impedance was maintained below 3000 ohms. Individual sweeps of time-locked EEG activity were recorded, amplified, analog filtered (1-70 Hz, 24 dB/octave slope), and digitized at an A/D rate of 500/sec with a PC-based NeuroScan system and SynAmps 16-bit amplifiers. The digitized epochs were averaged off-line, and filtered digitally (1-35 Hz, 24 dB/octave). The 50-ms prestimulus recording was used to establish a baseline to correct for the DC level of background EEG activity. The voltages from the prestimulus data points were averaged and then subtracted from the single sweeps of epoched EEG files prior to averaging. Ocular movement artifacts were digitally removed from the epochs (Semlitsch, Anderer, Schuster, & Presslich, 1986). Epochs containing artifacts exceeding +/- 50 microvolts were rejected from averaging.

Although different procedures have been used (e.g., Kraus, McGee, Carrell, Sharma, Micco, & Nicho, 1993a,b; Sharma, Kraus, McGee, Carrell, & Nicol, 1993; Dalebout & Fox, 2000) for defining the MMN waveform, the present investigators chose to define it in terms of voltage negativity in individual difference waves relative to baseline. The procedure for performing baseline corrections with the NeuroScan system used in the present study involves averaging the voltages from the prestimulus data points and then subtracting these data from the single sweeps of epoched EEG files prior to averaging. MMN peak amplitude was defined as the maximum negative peak between 100 and 400 msec. MMN onset and offset latencies were defined as the first points preceding and following this negative peak where the waveform intersected baseline. To examine possible differences between the three MMN extraction techniques and effects related to differences in ISIs used in the three deviant-alone test conditions, MMN amplitude areas were calculated. Amplitude area was defined in msec X microvolts for the area under the line drawn from the MMN onset to offset points. For this computation, waveform data (i.e., latency and amplitude coordinates) were

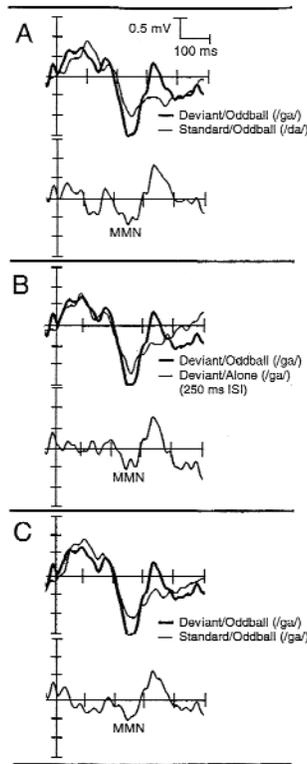


Figure 1. Mismatch Negativity (MMN) responses derived with each of three EEG extraction procedures. Shown are group-averaged waveforms from 12 young adults. A = Deviant-in-oddball (DO) extraction procedure; B = Deviant-alone (DA) method; C = Flip-flop (FF) MMN extraction method.

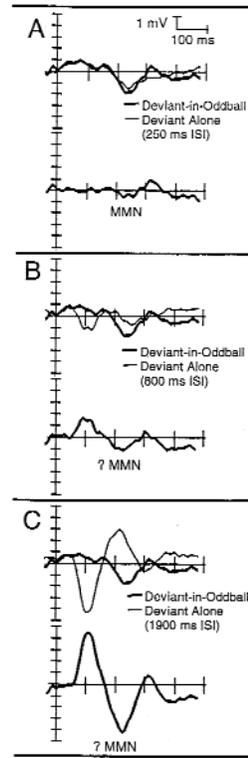


Figure 2. Effects of changing interstimulus intervals (ISIs) on the MMN responses (group-averaged waveforms) derived with the Deviant-Along (DA) MMN extraction technique. ISIs of (A) 250, (B) 800, and (C) 1900 msec were used during individual deviant-alone test runs. The overlaid group-averaged ERPs are shown at the top of each sub-figure, while the difference waves are shown at the bottom.

converted to ASCII format and exported for area analyses. The respective waveform peaks were independently selected by each of four experienced examiners (CRD, MC, LJW, and JLC) with a required three-quarters consensus.

RESULTS

Figure 1 shows the overlaid grand-averaged group waveforms along with the difference waves for each of the three

MMN extraction techniques. Figure 2, in contrast, shows the respective responses obtained with the deviant-alone method when two longer (i.e., 800 and 1900 msec) ISIs were employed in deviant-alone test runs. Table 2 shows the means and standard deviations of the amplitude area data obtained with each of the five MMN extraction procedures.

Two one-way repeated-measures analyses of variance (ANOVAs) were used to analyze the present data. All analyses were performed using a statistics computer

Table 2. Shows the means and standard deviations (in microvolts) of the area data obtained with each of the five MMN extraction procedures.

	MMN Extraction Procedure				
	DO	FF	DA (250)	DA (800)	DA (1900)
Mean	40.8	34.7	32.6	65.1	155.7
SD	23.4	27.1	39.1	66.1	120.0

Note: For the DA extraction procedure, three ISIs were used (250 msec, 800 msec, 1900 msec)

software package (SPSS for Windows, Releases 6.14 and 9.0.0). Relative treatment magnitude sizes (i.e., the proportion of variation “explained” by the independent variable) are indexed by omega-squared (ω^2) values (Keren & Lewis, 1979; Keppel, 1991). Omega-squared values of .01, .06, and .15 are considered to represent small, medium, and large effect sizes, respectively (Cohen, 1977). The first ANOVA compared the MMN amplitude areas for the three different MMN extraction procedures. This analysis only included the Deviant-Alone (DA) test which used 250 msec ISIs on deviant alone test runs, since this has been how the paradigm has been traditionally used in other laboratories (e.g., Kraus, McGee, Sharma, Carrell, & Nicol, 1992). As expected, no significant differences [$F(2,22) = .323$, Greenhouse-Geisser $p = .67$, $\omega^2 = .057$] were found among the three extraction procedures. The second ANOVA examined possible differences in amplitude area with the DA method that involved ISIs of 250, 800, and 1900 msec on the different deviant alone test runs. A significant main effect [$F(2,22) = 9.79$, Greenhouse-Geisser $p = .003$, $\omega^2 = 0.41$] was found. Post hoc tests in the form of two orthogonal single-df contrasts were performed to evaluate differences in mean MMN amplitude area with the deviant-alone method as a function of ISI. There was no statistically significant difference between the 250 msec and 800 msec ISI conditions (Greenhouse-Geisser $p = .26$). However, the amplitude areas found with both the 250 and 800 msec ISI conditions were statistically smaller than the 1900 msec ISI condition (Greenhouse-Geisser $p \leq .001$).

DISCUSSION

The present study, which used speech stimuli (/da/ and /ga/ syllabic events), replicated the findings of the earlier study by Walker et al. (2001) that used pure tone stimuli (1100 and 1000 Hz). Except for the use of different test stimuli, all other behavioral, recording, and analysis procedures were similar for the two projects.

As shown in Figure 1, the group-averaged difference waveforms provided evidence that MMNs to speech stimuli occurred with each of the three most common experimental protocols that have been developed to extract this response from EEG activity. The authors’

earlier study (Walker et al., 2001) obtained similar findings using tonal stimuli. These research findings are similar to those of numerous previous investigations (Naatanen & Kraus, 1995; Picton et al., 2000) which were interpreted as supporting the existence of some form of preconscious endogenous neural process in the brain in which specialized neural units become conditioned to respond to stimulus change. However, additional findings from both the earlier Walker et al. and the present study provides strong evidence that ISI-dependent neural refractory or recovery effects may, with some experimental protocols, overlay and modify the apparent morphology of the MMN response.

Examination of Figure 2 shows that, with the deviant-alone (DA) method of recording MMNs, changes in ISIs on the deviant alone test runs can dramatically alter the morphology of the resulting difference waves. With longer ISIs (i.e., 800 and 1900 msec), difference waves with successively higher negative peak amplitudes occur in the same approximate latency range as found with the shorter 250 msec ISI condition. Because of the presence of neural refractory or recovery effects, it would appear that the deviant-alone method can be problematic with respect to extracting the MMN response. When deviant stimuli are presented alone, the amplitudes of the elicited exogenous N1 and P2 components of the LAEP are strongly influenced by neuronal refractory or recovery effects. When deviant stimuli are presented in the context of ongoing standard stimuli, as occurs with the flip-flop and deviant-in-oddball experimental protocols, neural influences other than neural refractoriness may come into play.

The present authors wish to emphasize that the results of the Walker et al. (2001), study combined with the present findings, should not be construed as evidence against the attention/memory interpretation of the underlying nature of the MMN phenomenon. Rather, this new data provides strong evidence that neural refractory (plus habituation) effects associated with different ISIs can, with some experimental paradigms, contribute to the morphology of the derived MMN response. The present investigators’ strongly believe that whether the mismatch negativity phenomenon is the result of neural refractoriness or some form of endogenous

process, such as the activation of specially conditioned stimulus change or comparator units (or “deviance detectors”, e.g., Winkler, Karmos, & Naatanen, 1996), is an issue that is still unresolved. Because the vast majority of earlier MMN investigations (Naatanen, 1992; Kraus & Naatanen, 1995; Picton et al. 2000) used test paradigms that involved differences in ISIs between standard and deviant sounds, neural refractoriness may have been an uncontrolled variable in many of these studies. There is substantial evidence that, in all sensory modalities, the later the occurrence of the neural components, the more prolonged are the refractory periods (Allison, 1962). The N1 and P2 components of the LAEP have been reported to have recovery periods of seven seconds or longer (e.g., Nelson & Lassman, 1973; Picton, Woods, Baribeau-Braun, & Healey, 1976). Since the longest ISI with which MMNs can be successfully recorded is at least ten seconds long (Bottcher-Gandor & Ullsperger, 1992; Sams et al., 1993; Schroger & Winkler, 1995), this temporal overlap in the two respective functions opens the possibility that the two neural processes could be functionally related.

Since the identification of the MMN phenomenon in the mid to late 70s, numerous experiments (e.g., Naatanen, 1992; Picton et al. 2000) have been reported that, on the surface, appear to clearly support the attention/memory interpretation of the phenomenon over that of the activation of new neural units. For example, earlier studies by Naatanen et al. (1989a,b) provided evidence that the MMN response can be elicited by deviant stimuli that involve decreases in intensity as well as temporal duration. Other studies (Nordby et al., 1991) used deviants that were part of a serial tone pattern, in which one component of the standard stimulus pattern was omitted and the remaining portion of the stimulus served as the deviant. The MMN has also been elicited by an occasional too early stimulus in a stimulus sequence (Ford & Hillyard, 1981; Hari, Joutsiniemi, Hamalainen, & Vilkmann, 1989; Naatanen, Jiang, Lavikainen, & Reinikainen, 1993), by simple omission in a rapid-rate stimulus sequence (Yabe, Tervaniemi, Reinikainen, & Naatanen, 1997), or by the omission of the second member of a closely spaced tone pair (Tervaniemi, Saarinen, Paavilainen, Danilova, & Naatanen, 1994). Finally, there have also

been a few studies (see Picton et al., 2000) that demonstrated the occurrence of a MMN response in test paradigms that did not even use a standard stimulus per se, but either a standard feature or an abstract rule. All of these findings, plus many more too numerous to cite here, are difficult to explain in terms of the activation of new afferent neural units.

However, in recent years there has been a surge of new animal research which indicate that the numbers of distinct neural populations in the brain that are selectively tuned to various simple and complex features of sounds may be far more extensive than previously believed (Covey, 2000). Single unit studies with a variety of mammalian species (bats, cats, chinchillas, monkeys) have reported evidence for the existence of both intensity-specific (Phillips & Orman, 1984; Phillips, Orman, Musicant, & Wilson, 1985; Phillips, Sample, & Kitzesd, 1995; Pflugst & O'Connor, 1981; Suga & Manabe, 1982) and duration-specific (Brand, Urban, & Grothe, 2000; Casseday, Ehrlich, & Covey, 2000; Covey, 2000; Ehrlich, Casseday, & Covey, 1997; Guang-Di, 1998; He, Hashikawa, Ojima, & Kinouchi, 1997) single units in the brain. Thus, the present investigators believe that insufficient research information is currently available to determine how much of a difference or what kinds of differences are needed between standard and deviant stimuli before different populations of neural units would be activated. The activation of special neural units that are selectively tuned to stimulus “change”, as required by current attention theories of the MMN process, could be only one of many possible complex tuning mechanisms that exist in the brain.

REFERENCES

- Allison T. (1962). Recovery functions of somatosensory evoked responses in man. *Encephalography and Clinical Neurophysiology* 14:331–343.
- American Speech and Hearing Association. (1990). Guidelines for screening for hearing impairments and middle ear disorders. *ASHA* 32 (Suppl. 2):17- 24.
- Alho K, Sainio K, Sajaniemi N, Reinikainen K, Naatanen R. (1990). Electrical brain response of human newborns to pitch change of an acoustic stimulus. *EEG & Clin Neurophysiol* 77:151-155.
- Bottcher-Gandor C, Ullsperger P. (1992). Mismatch negativity in event-related potentials to auditory stimuli as a function of varying interstimulus interval. *Psychophysiology* 29:546 - 550.

- Brand A, Urban A, Grothe B. (2000). Duration tuning in the mouse auditory midbrain. *Journal of Neurophysiology* 84:1790-1799.
- Budd TW, Barry RJ, Gordon E, Rennie C, Michie PT. (1998). Decrement of the N1 auditory event-related potential with stimulus repetition: habituation vs. refractoriness. *International Journal of Psychophysiology* 31:51-68.
- Butler RN. (1973). The cumulative effects of different stimulus repetition rates on the auditory evoked response in man. *Electroencephalography and Clinical Neurophysiology* 35:337-345.
- Casseday JH, Ehrlich D, Covey E. (2000). Neural measurement of sound duration: control by excitatory-inhibitory interactions in the inferior colliculus. *J Neurophysiol* 84:1475-1487.
- Cohen J. (1977). *Statistical Power Analysis for the Behavioral Sciences*. Rev. ed. New York: Academic Press.
- Covey E. (2000). Neural population coding and auditory temporal pattern analysis. *Physiol Behav* 69:211-220.
- Dalebout S, Fox, L. (2000). Identification of the mismatch negativity in the responses of individual listeners. *J Amer Acad Audiol* 11:12-22.
- Ehrlich D, Casseday JH, Covey E. (1997). Neural tuning to sound duration in the inferior colliculus of the big brown bat, *ptesicus fuscus*. *J Neurophysiol* 1997:2360-2372.
- Ford JM, Hillyard SA. (1981). Event related potentials, ERPs, to interruptions of steady rhythm. *Psychophysiology* 18:322-330.
- Guang-Di, Chen A. (1998). Effects of stimulus duration on responses of neurons in the chinchilla inferior colliculus. *Hear Res* 122:142-150.
- Hari R, Joutsiniemi S-L, Hamalainen M, Vilkmann V. (1989). Neuromagnetic responses of human auditory cortex to interruptions in a steady rhythm. *Neurosci Lett* 99:164-168.
- He JF, Hashikawa T, Ojima H, Kinouchi Y. (1997). Temporal integration and duration tuning in the dorsal zone of cat auditory cortex. *Journal of Neuroscience* 17:2615-2625.
- Hillyard S, Hink RF, Schwent VL, Picton TW. (1973). Electrical signs of selective attention in the human brain. *Science* 182:177-180.
- Kane NM, Curry SH, Butler SR, Cummins BH. (1993). Electrophysiological indicator of awakening from coma. *The Lancet* 341, 688.
- Keppel G. (1991). *Design and Analysis: A Researcher's Handbook*. 3rd ed. Upper Saddle River, NJ: Prentice Hall.
- Keren G, Lewis C. (1979). Partial omega squared for ANOVA designs. *Educational and Psychological Measurement* 39:119 - 128.
- Kraus N, McGee TJ, Sharma A, Carrell TD, Nicol TG. (1992). Mismatch negativity event-related potentials to speech stimuli. *Ear and Hear* 13:158-164.
- Kraus N, McGee TJ, Micco AG, Carrell T, Sharma A, Nicho TG. (1993a). Mismatch negativity in school-age children to speech stimuli that are just perceptibly different. *Electroencephalography and Clinical Neurophysiology* 88:123-130.
- Kraus N, McGee TJ, Carrell T, Sharma A, Micco AG, Nicho TG. (1993b). Speech-evoked cortical potentials in children. *J Amer Acad Audiol* 4:238-248.
- Naatanen R. (1992). *Attention and Brain Function*. Hillsdale, NJ: Erlbaum.
- Naatanen R, Kraus N, eds. (1995). Mismatch negativity as an index of central auditory function. *Ear and Hear* 16:1-146.
- Naatanen R, Teder W. (1991). Attention effects on the auditory event-related potential. *Acta Otolaryngol Suppl* 491:161-167.
- Naatanen R, Gaillard AWK, Mantysalo S. (1978). Early selective attention effect on evoked potential reinterpreted. *Acta Psychol* 42:313-329.
- Naatanen R, Paavilainen P, Alho K, Reinikainen K, Sams M. (1989a). Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? *Neurosci Lett* 98:217-221.
- Naatanen R, Paavilainen P, Alho K, Reinikainen K, Sams M. (1989b). Event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man. *Neurosci Lett* 107:347-352.
- Naatanen R, Jiang D, Lavikainen J, Reinikainen K, Paavilainen P. (1993). Event-related potentials reveal a memory trace for temporal features. *Neuroreport* 5:310-312.
- Nelson DA, Lassman FM. (1968). Effects of inter-signal interval on the human auditory evoked response. *J Acoust Soc Amer* 44:1529-1532.
- Nelson DA, Lassman FM. (1973). Combined effects of recovery period and stimulus intensity on the human auditory-evoked vertex response. *Journal of Speech and Hearing Research* 16:297-308.
- Nelson DA, Lassman FM. (1977). Re-examination of the effects of periodic and aperiodic stimulation on the auditory-evoked vertex response. *Audiology* 16:409-418.
- Nielsen-Bohlman, Knight RT, Woods DL, Woodward K. (1988). Differential processing of auditory stimuli continues during sleep. *Neuroscience Abstracts*.
- Nordby H, Hammerborg D, Roth WT, Hugdahl K. (1994). ERPs for infrequent omissions and inclusions of stimulus elements. *Psychophysiology* 31(5):544-552.
- Novak G, Ritter W, Vaughan H. (1992). The chronometry of attention-modulated processing and automatic mismatch detections. *Psychophysiology* 29:412-430.
- Pfingst BE, O'Conner TA. (1981). Characteristics of neurons in auditory cortex of monkeys performing a simple auditory task. *J Neurophysiol* 45:16-34.
- Phillips DP, Orman SS. (1984). Responses of single neurons in posterior field of cat auditory cortex to tonal stimulation. *J Neurophysiol* 51:147-163.

Phillips DP, Orman SS, Musicant AD, Wilson GF. (1985). Neurons in the cat's primary auditory cortex distinguished by their responses to tones and wide-spectrum noise. *Hear Res* 18:73-86.

Phillips DP, Semple MN, Kitzes LM. (1995). Factors shaping the tone level sensitivity of single neurons in posterior field of cat auditory cortex. *J Neurophysiol* 73:674-686.

Picton TW, Rodriquez R, Linden R, Maist A. (1985). The neurophysiology of human hearing. *Human Communication Canada* 9:127-136.

Picton TW, Alain C, Otten L, Ritter W, Achim A. (2000). Mismatch negativity: Different water in the same river. *Audiol Neurootol* 5:111-139.

Semlitsch HV, Anderer R, Schuster P, Presslich O. (1986). A solution for reliable and valid reduction of ocular artifacts applied to the P300 ERP. *Psychophysiology* 23:695-703.

Sharma A, Kraus N, McGee TJ, Carrell TD, Nicol T. (1993). Acoustic versus phonetic representation of speech as reflected in mismatch negativity event-related potentials. *Electroencephalography and Clinical Neurophysiology* 88:64-71.

Schroger E, Winkler I. (1995). Presentation rate and magnitude of stimulus deviance effects on human pre-attentive change detection. *Neurosci Lett* 193:185-188.

Squires KC, Hecox KE. (1983). Electrophysiological evaluation of higher level auditory processing. *Seminars in Hearing* 4:415-433.

Suga N, Manabe T. (1982). Neural basis of amplitude-spectrum representation in auditory cortex of the mustached bat. *J Neurophysiol* 47:225-255.

Sutton S, Braren M, Zubin J, John ER. (1965). Evoked potential correlates of stimulus uncertainty. *Science* 150:1187-1188.

Tervaniemi M, Saarinen J, Paavilainen P, Danilova N, Naatanen R. (1994). Temporal integration of auditory information in sensory memory as reflected by the mismatch negativity. *Biology Psychology* 38:157-167.

Walker LJ, Carpenter M, Downs CR, Cranford JL, Stuart A, Pravica D. (2001). Possible neuronal refractory or recovery artifacts associated with recording the mismatch negativity response. *J Amer Acad Audiol* 12:348-356.

Winkler J, Karmos G, Naatanen R. (1996). Adaptive modeling of the unattended acoustic environment reflected in the mismatch negativity event-related potential. *Brain Research* 742:239-252.

Yabe H, Tervaniemi M, Reinikainen K, Naatanen R. (1997). Temporal window of integration revealed by MMN to sound omission. *Neuroreport* 8:1971-1974.