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Long-term habituation of the speech-elicited mismatch negativity

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Abstract

A significant issue in the use of the mismatch negativity evoked potential (MMN) concerns its low signal-to-noise ratio (SNR). One can improve the noise level by increasing the number of samples included in the averaged response. However, improvement achieved in this way assumes that the signal, the MMN, remains stable for extended test times, an assumption which has not been tested. If the MMN is not stable, or exhibits habituation over the test session, then SNR would be adversely affected. MMN response magnitude was measured in 5-min intervals over the course of a test session in response to various speech syllable contrasts. Significant long-term habituation of MMN was observed for all three subject populations tested: young adults, school-age children, and guinea pigs. The time course of the habituation and the stimulus conditions under which it occurs have important implications for research and clinical applications of the MMN. Recording procedures that minimize habituation effects may be used to advantage to improve the signal-to-noise ratio of the MMN.

Descriptors: Auditory evoked potential, Mismatch negativity, Habituation

The mismatch negativity (MMN) is an evoked potential that is elicited by a sequence of repeated stimuli in which an "odd" or "rare" stimulus occurs on a low percentage (~10–15%) of presentations. The MMN has been purported to be an objective and sensitive measure of processes associated with auditory discrimination of both simple and complex signals, because it is the change in the stimulation which triggers the occurrence of the MMN. That is, the MMN appears to index the discrimination of an acoustic difference (rather than simply a detection of an acoustic event). The response has the practical advantage that it can be elicited in young children even under conditions of inattention, raising hope that the MMN is amenable to clinical use, particularly in cases of children with central auditory disorders (Kraus et al., 1993, 1996).

A significant issue to be resolved, however, concerns the signal-to-noise ratio (SNR) of the MMN. It has been noted by Lang et al. (1995), Kurtzberg et al. (1995), and McGee, Kraus, & Nicol (1997) that the SNR of the MMN is relatively low given the recording procedures usually described (Kraus et al., 1993). The SNR is sufficient for obtaining group grand averages, but responses from individual subjects are difficult to interpret. Thus, the described procedures result in responses that may not be useful for studies in which measurements from individuals are at issue. The low SNR also affects clinical applications. If responses are noisy and of low amplitude even in normal subjects how can we have confidence in interpreting adversely affected responses from impaired individuals?

The obvious answers to this dilemma include reducing the noise level, increasing the signal level, or both. Lowering the noise level may be accomplished by increasing the number of samples included in the averaged response. This would extend the testing time, possibly a necessary step to obtain a sufficient SNR. However, improvement achieved in this way assumes that the signal, the MMN, remains stable for extended test times. Although such stability appears to be characteristic of some obligatory responses, such as auditory brain stem and middle latency responses, Woods and Elmasian (1986) have shown that certain cortical responses (N1 and P3a) show considerable long-term habituation. We cannot assume a priori that long-term stability characterizes the MMN. The purpose of the described study was to investigate the stability of the MMN across the time course of a typical testing session. Because this is part of a larger study investigating speech perception, responses were elicited by speech syllables. Responses are described from three subject populations: adults, school-age children, and guinea pigs.

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Methods

Data Sets

Data sets were derived from four studies that have been accomplished in our laboratory. Two of these studies compare MMNs to phonemic contrasts (/wa/-/ba/, /da/-/ga/) at two difficulty levels

Table 1. *Studies*

Study	Subjects	Female/Male	Rare-Freq.	Conditions
1	Children (6–14 years)			
	$N = 22$/group, 2 groups	22/22	/da/-/ga/$_2$	Easy discrimination
	$N = 19$/group, 2 groups	20/18	/da/-/ga/$_1$	Difficult discrimination
2	Children (6–14 years)			
	$N = 23$	12/11	/wa/-/ba/$_2$	Easy discrimination
	$N = 38$	21/17	/wa/-/ba/$_1$	Difficult discrimination
3	Adults (22–33 years) $N = 14$	8/6	/da/-/ga/$_1$	Difficult discrimination
4	Guinea pigs (0.3–0.4 kg) $N = 10$	0/10	/da/-/ga/$_1$	Ss anesthetized

of discrimination, very near to discrimination threshold (difficult), and at a level easily discriminated (easy; Kraus et al., 1996). One study considered the adult response to a /da/-/ga/ contrast, just better than discrimination threshold. In a fourth study, MMNs to /da/-/ga/ were obtained from anesthetized guinea pigs. Table 1 lists the subjects' numbers and ages for each group. A sufficient number of children were available for the /da/-/ga/ contrast so that two groups could be formed for each difficulty level. Children were assigned to groups so that the groups were matched for MMN amplitude. Thus the average MMN amplitude across subjects was equivalent for each difficulty level.

All human subjects had tone thresholds better than 20 dB HL for 500–8000 Hz, and tympanograms were normal. All subjects showed a recognizable MMN, with an onset latency of 140–220 ms, to the stimulus pairs used in the study. Children were considered "normal" based on performance within normal limits on cognitive, learning, attention, and hearing tests and on their histories as reported by parents (Kraus et al., 1996). All children were academically at their appropriate grade level. The children's ages (6–14 years) encompass a period during which the speech-elicited MMN shows no developmental changes (Kraus, Koch, McGee, Nicol, & Cunningham, 1999). Adults were masters and doctoral students, ages 22–33. All guinea pigs were healthy and showed ABR click thresholds better than 10 dB SPL.

Stimuli

Speech stimuli were used because this is part of a larger series of studies concerning the central auditory processing of acoustic elements of speech (Kraus et al., 1996). Stimuli were generated on a Klatt synthesizer and were composed of five formants (F_1–F_5). For all stimuli, the fundamental frequency ramped linearly from 103 to 125 Hz over the first 35 ms, then to 83 Hz over the remainder of the syllable. Formants F_4 and F_5 were held constant at 3600 and 4500 Hz, respectively. Voice onset was immediate, and stimulus duration was 100 ms.

For /da/ and /ga/, vowel formant frequencies were 720, 1240, and 2500 Hz for F_1, F_2, and F_3, respectively. Onset frequencies were 220 and 1700 Hz for F_1 and F_2, respectively. F_3 onset frequency was 2580, 2500, and 2300 Hz for /da/, /ga/$_1$, and /ga/$_2$, respectively. Formant transition duration was 40 ms.

For /ba/ and /wa/, vowel formant frequencies were 769, 1232, and 2862 Hz for F_1, F_2, and F_3, respectively. Onset frequencies were 234 and 1700 Hz for F_1 and F_2, respectively. Formant transition durations were 40, 35, and 25 ms for /wa/, /ba/$_1$, and /ba/$_2$, respectively.

In a group of normal adult subjects, /ga/$_1$ and /ga/$_2$ were behaviorally discriminable from /da/ with d′ values of 0.86 and 2.56, respectively. For the children in this study, 98% had just noticeable differences (jnds) better than the /ga/$_2$-/da/ contrast, and 44% had jnds better than the /ga/$_1$-/da/ contrast. Thus, we call /ga/$_2$-/da/ an "easy" to discriminate contrast, and /ga/$_1$-/da/ a "difficult" to discriminate contrast. For normal adults, /ba/$_1$ and /ba/$_2$ were behaviorally discriminable from /wa/ with d′ values of 1.2 and 2.7, respectively. For the children in this study, 98% had jnds better than the /wa/-/ba/$_2$ contrast, and 40% had jnds better than the /wa/-/ba/$_1$ contrast.

Human MMN Collection

Responses for Studies 1 and 3 were collected on a Neuroscan Scan system. Silver–silver-chloride recording electrodes were positioned at 11 locations: Fz, F3, F4, Cz, Pz, A1, A2, two positions slightly anterior to T4 and T5 (all noninverting), nosetip (inverting), and Fpz (ground). For Study 2, responses were collected on a Biologic system, from electrodes at Fz (noninverting), right earlobe (inverting), and Fpz (ground). The current report focuses on responses from the Fz electrode. Eye movements were monitored with a bipolar electrode montage (supraorbital-to-lateral canthus). Prior to data collection, subjects were instructed to blink and move their eyes while amplifier settings were adjusted to ensure detection of eye movements. During data collection, subjects watched a movie (on video) of his/her choice. The sound level of the movie was adjusted to less than 40 dB HL. Test stimuli were delivered to the right ear, and the left ear was left unoccluded so that subjects could hear the movie. This ensured that subjects did not doze during testing. Nor did subjects pay attention to test stimuli. In fact, subjects were engrossed in the movie and usually stayed past the end of testing to finish watching.

The recording window included a 90-ms prestimulus period and 500-ms poststimulus time, with an A/D conversion rate of 1,000 pts/s for the /da/-/ga/ conditions. For /ba/-/wa/, the prestimulus period was 100 ms, and the A/D conversion rate was 853 pts/s. Evoked responses were analog lowpass filtered on-line at 100 Hz, and were digitally filtered off-line with a bandpass of 0.1 to 100 Hz. Sweeps in which activity exceeded $\pm 100\ \mu$V were rejected from the average off-line. This served to eliminate eye movements and other large artifacts. Each test session lasted approximately 90 min, including electrode preparation, equipment setup and subject instructions, and data collection. For the children, the goal was to collect data in the MMN sequence for 35–40 min, although if a subject began to appear restless after 30 min, MMN collection would be terminated and the rare-alone presentation begun. The adult MMN data were collected for 20 min, a 10-min break was given, and MMN data were then collected for an additional 20 min. During the break, subjects walked around

and chatted with laboratory personnel. Electrode impedance was checked before resuming data collection.

Stimuli were presented to the right ear at 75 dB SPL through insert earphones without pausing at a rate of 1.7 stimuli/s (/ga/-/da/) or 1.4 stimuli/s (/ba/-/wa/). A PC-based system (Neuroscan Stim) controlled the timing of stimulus presentation and delivered an external trigger to the evoked potential system. For each MMN, stimuli were presented, without pause or rest break, with a rare probability of 10% (/ga/-/da/, where /da/ is rare) or 15% (/ba/-/wa/, where /wa/ is rare). At least three standard stimuli preceded each presentation of the rare stimulus. Twenty standard stimuli preceded the occurrence of the first rare stimulus. Responses to standard stimuli immediately following rare stimuli were excluded from the standard stimulus average.

Responses also were obtained to a sequence in which the rare stimulus (/da/ or /wa/) was presented repetitively for approximately 20 min, about 2,000 trials (rare alone). It is common practice to view the MMN in a difference wave calculated by subtracting the standard response from the response to the rare stimulus. However, that difference wave will include not only the MMN, but also any inherent response differences to the two stimuli. We have preferred to view the MMN by calculating a difference between the responses to a stimulus presented as a rare and that same stimulus presented alone in a repetitive sequence. Thus a difference wave is obtained which is not confounded by inherent stimulus differences. Also, this procedure eliminates the need to acquire data with the rare and standard stimuli reversed, thus saving time in the test procedure.

Guinea Pig MMN Collection

Animals were anesthetized with ketamine hydrochloride (100 mg/kg) and xylazine (7 mg/kg), and maintained at a body temperature of 37.5°C (±1°C). Smaller doses (15 mg/kg ketamine; 3 mg/kg xylazine) were administered as needed for the rest of the experiment. Epidural silver bead electrodes (0.5 mm diameter) were positioned on the epidural surface on the midline, 10 mm caudal to bregma and 1 mm to the left of the sagittal suture. The ground electrode was positioned approximately 15 mm rostral to bregma, just right of midline. All stimuli were presented to the right ear at 85 dB SPL. Signals were delivered through hollow earbars in a stereotaxic device using ER-3 insert earphones. Responses were band-pass filtered at 0.05–500 Hz. Stimulus delivery was otherwise the same as for the human studies.

MMN Analysis

Responses were averaged, across subjects, for each group, for successive 5.5-min intervals. Because 5.5 min is not long enough to collect a sufficient number of averages in an individual to assess MMN, the reader should keep in mind that all measurements were made from grand average waveforms rather than individual responses. A typical 5.5-min interval results in about 50 (±7) responses to the deviant stimuli. The MMN response area was measured by the following method. Waveforms were baselined to the average of the prestimulus period. For each group average, an obvious negativity was apparent on the difference wave for the first 5.5-min interval. MMN onset latency was defined as the point at which, after the P1N1 complex, this difference wave dropped below the baseline. Offset latency was defined as the point at which the waveform regained baseline, or at 500 ms if the waveform had not returned to baseline. Area was determined by calculating the integral over this interval. The integral then was determined for the same interval for that group for waveforms obtained in subsequent testing. That is, MMN interval was determined on the first 5.5-min waveform and the integral was computed for that same interval for all subsequent waveforms. This allowed an "MMN area" to be calculated on later waveforms in which an MMN was small or not apparent. Response habituation was assessed across studies.

Results

As shown in Figure 1a, MMN to /ga/$_2$-/da/ is readily apparent in children for group average responses obtained at 0–5.5 min, but no

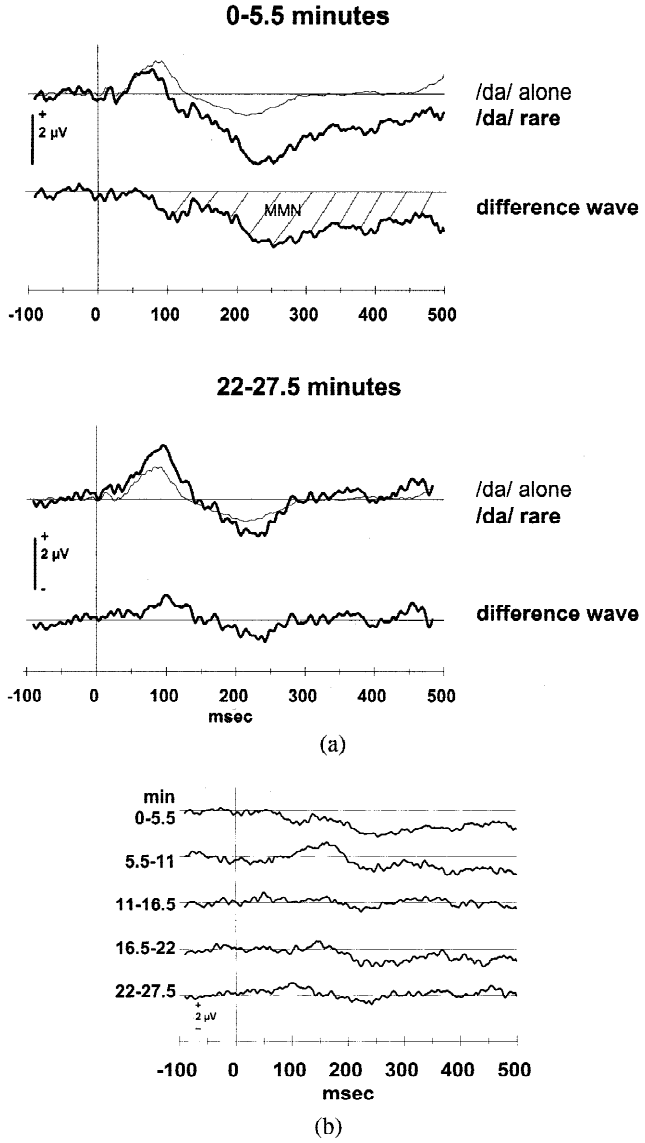

Figure 1. (a) Response from children to /da/ presented in series alone (top); response to /da/ presented as a rare stimulus in a sequence with /ga/$_2$ (middle); the difference wave obtained from subtracting the alone (top) waveform from the rare waveform (bottom). The shaded area in the top panel is the MMN (n = 44). Comparison of upper and lower panels shows a robust MMN at 0–5.5 min, but no MMN at 22–27.5 min. (b) Difference waves averaged across successive 5.5-min intervals in response to the easily discriminable contrast, /da/-/ga/$_2$ (N = 44). A large MMN is apparent in the first 5.5 min, but the MMN then diminishes.

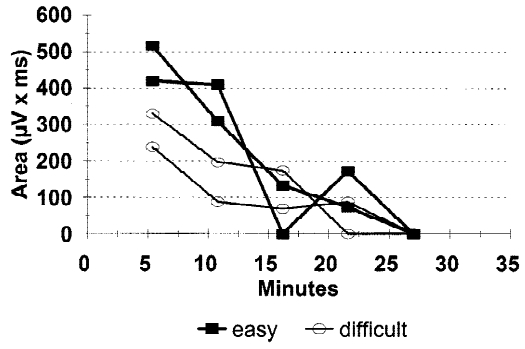

Figure 2. MMN area measurements across test time for two /da/-/ga/ contrasts. The thick lines represent results for the easily discriminable contrast, /da/-/ga/$_2$ (N = 22/group, 2 groups) and the thin lines represent results for the contrast that is difficult to discriminate, /da/-/ga/$_1$ (N = 19/group, 2 groups).

MMN is seen at 22–27.5 min. In this figure are shown the rare, alone, and the difference waves. Figure 1b demonstrates the progression of the habituation on the difference waveforms for each interval. A large MMN is apparent in the first time interval. Responses obtained later in the test session show either a smaller amplitude negativity or no negativity is apparent. There appears to some waxing and waning of the MMN. The 16.5–22-min waveform shows a recognizable MMN, while the preceding and following waveforms show no MMN. This was not a consistent finding.

In Figure 2, MMN area measurements are plotted across test time for two /da/-/ga/ contrasts, for the easily discriminable contrast, /da/-/ga/$_2$ (n = 22/group, two groups) and for the contrast that is difficult to discriminate, /da/-/ga/$_1$ (n = 19/group, two groups). Results indicate that MMN long-term habituation occurs for both easy- and difficult-to-discriminate contrasts.

MMN habituation was also observed in Studies 2 and 3. MMN area measurements over successive intervals recorded in young adults (n = 7) to the /da/-/ga/$_1$ contrast and in school-age children to the easily discriminated /wa/-/ba/$_2$ stimulus contrast show a similar decline over successive test intervals. Responses to the more difficult /wa/-/ba/$_1$ contrast did not show habituation overall. The initial response in the first 5.5 min was small, however. Given the presence of residual noise in the recordings, habituation likely would be less apparent in these data.

MMN habituation was observed in the results from guinea pigs in response to /da/-/ga/$_1$. As with humans, a robust MMN was observed at 0–5.5 min, but no MMN was apparent at 22–27.5 min (n = 10) (Figure 3a). Figure 3b shows the difference waveforms for guinea pigs in response to /da/-/ga/$_1$ at successive test times. A large MMN was apparent in the first time 5.5 min. By 11–16.5 min, the MMN response was minimal.

A plot of guinea pig MMN area measurements across test time further illustrates this point (Figure 4). Guinea pig responses are of larger amplitude due to the epidural recording site, but the pattern is similar to that of the children.

MMN area also was plotted for each group with area presented as a percentage of MMN area obtained for that group in the first 5-min test interval (Figure 5). These results indicate that long-term habituation demonstrates a similar pattern across populations and stimuli. Across studies, MMN habituation occurred by 15 min (Wilcoxon Signed Ranks Test, T^+ = 38; p = .0039).

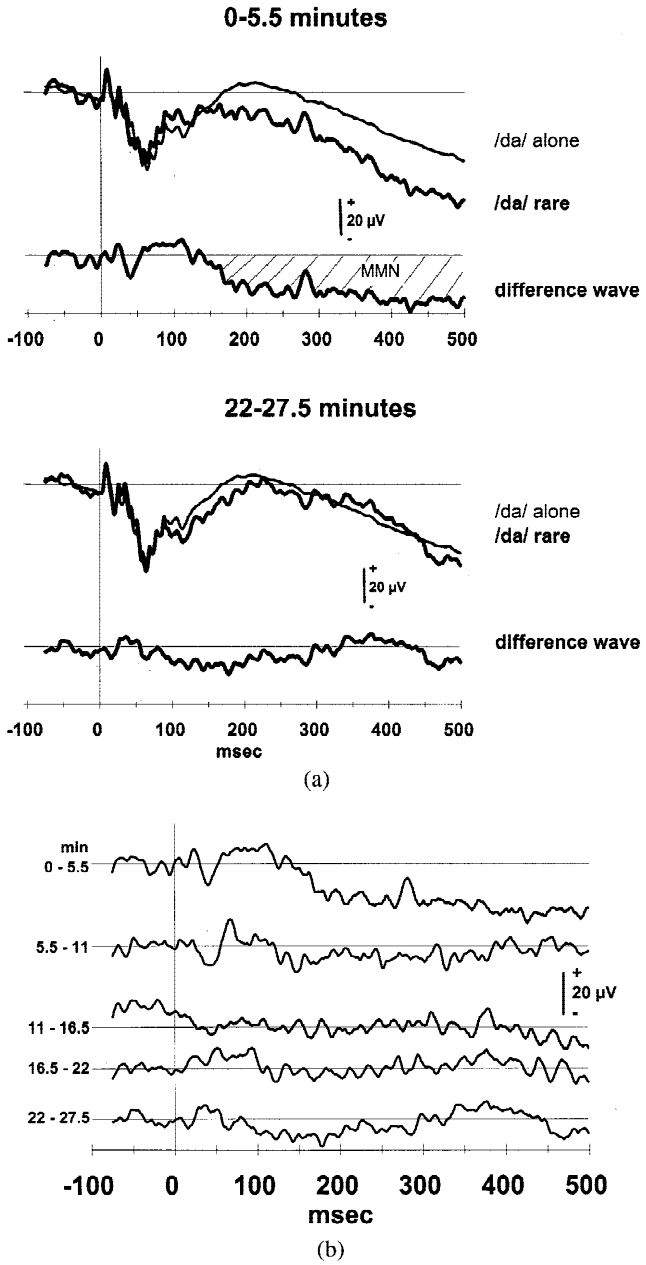

Figure 3. (a) Response from guinea pigs to /da/ presented in series alone (top); response to /da/ presented as a rare stimulus in a sequence with /ga/$_1$ (middle); the difference wave obtained from subtracting the alone (top) waveform from the rare waveform (bottom). The bottom waveform is the difference wave obtained from subtracting the alone (top) waveform from the rare (middle) waveform. The shaded area in the top panel is the MMN. Comparison of upper and lower panels shows a robust MMN at 0–5.5 min, but no MMN at 22–27.5 min (N = 10). (b) Difference waves averaged across successive 5.5-min intervals in response to the /da/-/ga/$_1$ contrast. A large MMN is apparent in the first 5.5 min, but the MMN then diminishes.

Given the consistent occurrence of habituation, the question arose as to whether a change in the test procedure could reenergize the MMN. To this end, MMNs were recorded to the contrast /da/-/ga/$_1$ in young adult subjects (n = 7) for two 20-min test sessions separated by a 10-min rest and recreation break (R&R).

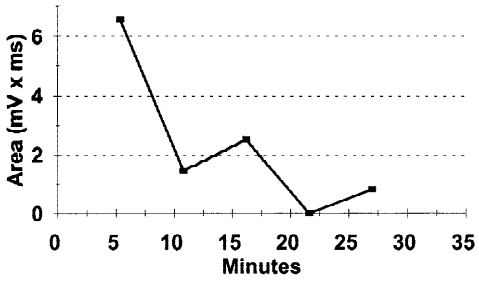

Figure 4. Guinea pig MMN area measurements across test time for the /da/-/ga/$_1$ contrast.

During the break, subjects left the test booth, walked around the laboratory, and socialized with researchers. As shown in Figure 6, during the first 20-min session, MMN area demonstrates a robust response in the first 5-min interval, but the MMN then diminishes rapidly. Following a 10-min break, the MMN recovers and then habituates again.

Discussion

For each group and for each speech stimulus contrast, MMN responses declined in magnitude from the beginning to the end of the test session. The decline occurred fairly rapidly, after only approximately 11 min of testing. The time course of MMN habituation is more rapid than for P3a, which declines after approximately 30 min (Woods & Elmasian, 1986). The decline in MMN is not perfectly systematic. Waxing and waning was observed in one group, and for one group with a near-threshold contrast, habituation was minimal. These effects were observed only for low amplitude responses. It cannot be readily determined whether these discrepancies represent restoration or maintenance of the MMN signal or are the spurious fluctuations of residual noise. Whereas drowsiness might cause a decrement in the MMN (Sallinen & Lyytinen, 1997), this could not explain our findings because subjects were highly attentive to an ongoing video and showed no evidence of drowsiness.

MMN habituation, of course, has important ramifications for MMN signal-to-noise ratio. Given that the MMN signal habituates, in any test in which response collection has extended longer than 10–15 min, the MMN magnitude will be disadvantaged. Although continued collection would reduce noise, MMN amplitude would also be in decline. In the averaging process, noise reduction occurs in proportion to the square root of the number of sample sweeps included in the average. MMN amplitude would decline according to its habituation function. In the worst case, with a very rapidly declining function, such that no MMN occurs, MMN signal strength in the averaged response would diminish linearly with the number

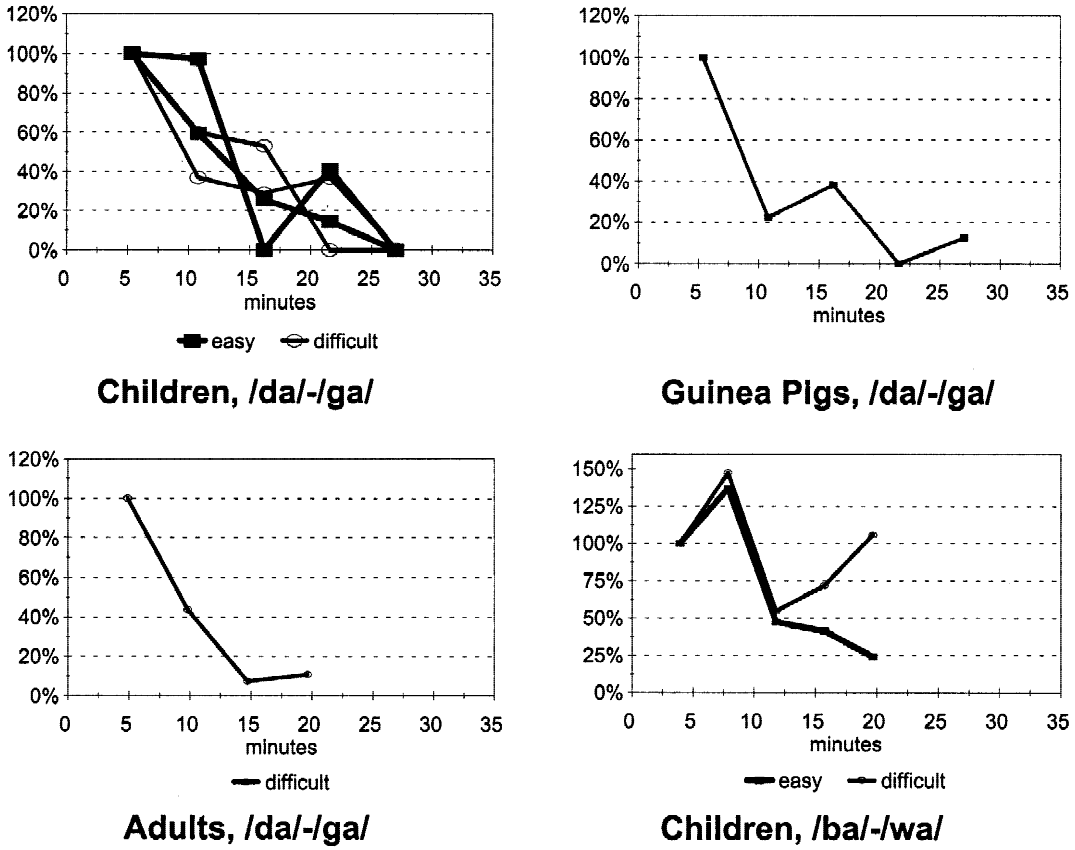

Figure 5. MMN area as a function of testing time for all populations and stimuli reported. Areas are presented as a percentage of MMN area obtained for the respective group in the first 5.5 min of the test session. Top: Specific area values are shown in Figures 2 and 4. Bottom: Starting areas were 375 μV $\times$ ms for adults, and 469 μV $\times$ ms and 214 μV $\times$ ms for easy and hard stimulus contrasts in children, respectively.

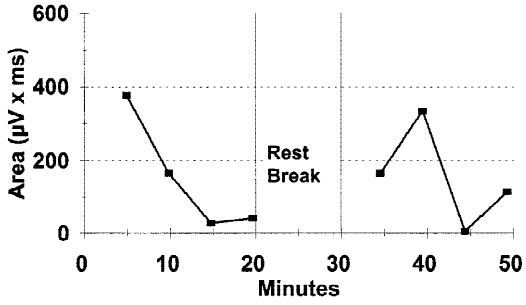

Figure 6. MMN area measurements over successive intervals recorded in young adults ($n = 7$) to the /da/-/ga/$_1$ contrast for two 20-min test sessions separated by a 10 min break. During the first test session, MMN area demonstrates a robust response in the first 5-min interval, but the MMN then diminishes rapidly. Following a 10-min break, the MMN recovers and then habituates again.

of sweeps. Thus, after a while, the signal would diminish more rapidly than the noise and SNR would worsen as averaging continues.

Given the typical stimulus presentation rates and rare probabilities used, at best only 100–125 rare stimuli could be presented in the 11 or so minutes before habituation begins to degrade the strength of the MMN response. Given the occurrence of eye blinks and periods of other noise, even fewer responses to rare stimuli would be included in the averaged response before the SNR would worsen because of declining signal strength. That is, MMN may be governed by a law of diminishing returns. An important topic for further research would be a determination of the test duration that would allow for the optimal SNR.

It should be noted that all subjects in the current study showed an MMN to the contrast tested, even though habituation had occurred. Even with the observed habituation, MMNs can be obtained, albeit with a poor signal-to-noise ratio. MMNs even show good reliability across test sessions on subsequent days (Escera & Grau, 1996; Tervaniemi et al., 1999; Tremblay, Kraus, & McGee, 1998). Yet, when subjects were given a rest break, MMN amplitude show a marked recovery. If the judicious use of rest periods consistently restores the MMN response, then MMN signal strength could be improved dramatically over current methods. The MMN restoration seen after the rest break suggests that it is possible for collection time to be extended, noise level reduced, and a sufficient SNR attained to better record MMN in individuals.

Of course, further questions must be answered. The current study utilized only speech stimuli. Whether such marked habituation is evident for other acoustic contrasts is an unresolved question. Importantly, the time course of the MMN restoration should be investigated, as well as whether there is an optimal balance between the stimulus presentation interval and the rest interval. Whether closely spaced short breaks or longer breaks would result in better recovery is a topic for further research. Whether recovery varies with population or stimulus is also in question. An extended study that examines these factors is beyond the scope of the current paper, but this does appear to be a promising future direction.

An evoked potential that is a response to a stimulus difference, that can be recorded even under conditions of inattention, and that is apparent in a difficult-to-test population such as young children is an exciting discovery. Thus, the MMN has generated considerable interest. An important component of that excitement is the possibility that the evoked potential can be used to assess discrimination in individual subjects or patients. A continuing effort to solve the difficulties associated with obtaining such recording is eminently worth the effort. MMN habituation appears to be a process that disadvantages MMN SNR. Working to understand the habituation process, and possible recovery processes, is very important to eventual clinical and research applications of MMN.

Conclusions

The speech-elicited MMN demonstrated long-term habituation for three populations: children, young adults, and guinea pigs. The time course of MMN habituation was rapid, with the MMN declining in a considerably shorter time than a typical test session. A short rest break, however, resulted in a recovery of the MMN response.

Despite habituation, all subjects showed an MMN to the contrast tested. Even with the observed habituation, MMNs can be obtained, albeit with a poor signal-to-noise ratio. If habituation can be reduced, then MMN signal-to-noise ratio very likely would be enhanced. An understanding of the MMN habituation process and discovering ways to strengthen the MMN response will enhance the prospects for further research and clinical applications of the MMN.

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