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Stability of mismatch negativities in children

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Abstract

Objectives and methods: Mismatch negativities (MMN) to frequency and duration changes in a series of repetitive tones and to two different consonant-vowel syllables (ba and ga, standard da) were recorded in a test and retest session in 15 children aged 7–11 years. Reliability within one session and stability between the sessions of MMN amplitudes and the ERP-components P1 and N1 were determined by correlation coefficients.

Results: Mean amplitudes of the grand averages showed a decrease of MMN during the second test session in a late latency window (400–500 ms) for the frequency MMN and of the MMN elicited by speech stimuli. The individual stability reached significance only for the duration deviant and one of the syllables. Compared to results found in adults with similar stimulus conditions the stability of the MMN in children seems to be somewhat lower. The components P1 and N1 to both stimulus types (tone and speech), however, showed a high reliability and individual stability.

Conclusion: While MMN is a useful tool to study processing deficits in groups of children, as e.g. in language-impaired children, MMN as a individual diagnostic measure should be interpreted very cautiously.

Keywords: Event-related potentials; Mismatch negativity; Children; Reliability; Stability

1. Introduction

The mismatch negativity (MMN) is an evoked cortical potential reflecting the outcome of an automatic comparison process between acoustic stimuli. It is elicited by a deviant stimulus in a sequence of identical sounds. The deviant may differ from the standard stimulus in frequency, duration, intensity or even more complex features. The MMN is obtained by subtracting the evoked response to the deviant stimulus from the standard response. Subjects do not have to pay attention to the stimulus sounds. During the last years a wide interest in clinical applications of the MMN in different areas such as adult psychiatry (e.g. alcoholism, aphasia and dementia; see Näätänen, 1995; Escera, 1997), child psychiatry (attention deficit disorder, Korpilahti and Lang, 1994; Kemner et al., 1995, 1996; autism, language-impairment, Holopainen et al., 1997; dyslexia, Schulte-Körne et al., 1998), audiology and even neurosurgery (Liasis et al., 1997) has developed. It was, therefore, suggested to be a very useful tool in identifying children at high risk for language disorders or dyslexia by assessing auditory processing deficits at an early age (Cheour et al., 1997; Leppänen and Lyytinen, 1997).

As a prerequesite for using it for individual diagnostic purposes it is necessary to determine its reliability and stability according to the standards for diagnostic tools as intelligence or language tests.

Pekkonen et al. (1995) studied the replicability of the MMN in 10 young adults. The correlations between the mean MMN-amplitudes of two test sessions (1 month apart) varied between deviant types (frequency vs. duration deviant), inter-stimulus-intervals (0.5 vs. 1.5 s) and electrode sites. The highest and only significant correlation ($r = 0.67$) was found for the duration deviant with an ISI of 0.5 s at F4. Kathmann et al. (1999) also found a higher stability for the duration deviant (0.56–0.72 at different electrodes) than for the frequency deviant (0.28–0.48) in 45 adults between two sessions (within 1 month). Escera and Grau (1996) repeated a MMN experiment using a frequency deviant after 2 h. The best short-term replicability was reached at F4 ($r = 0.59$) and C3 ($r = 0.66$). Joutsiniemi et al. (1998) found a rather low quantitative replicability (with $r = 0.363$ as the highest value) of the MMN to a duration deviant in 14 subjects. The interval between sessions in this study varied between 2 and 12 weeks and the age range was large (9–84 years). In an experiment in

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our laboratory which tested the stability of the MMN to pure tone and speech stimuli in adults (Uwer and von Suchodoletz, 1998), correlations also varied considerably between the stimulus types. So far, the stability of MMN measures in children has not been studied. Kurtzberg et al. (1995) described a high intra-individual variability in normal children over 10 runs of a MMN experiment. However, they observed that the MMN in this group of 8 year old children was more stable than in younger children or infants. Therefore, it can be expected that the retest-reliability in children will not reach the level of adults.

Determining the stability of the components of the waveforms from which the MMN is derived by subtraction could help to decide whether a possible low stability of the MMN is due to a low replicability of the standard and deviant evoked responses or rather to a instability of the MMN itself. Pekkonen et al. (1995) reported a higher replicability of the N100 amplitude compared to the MMN only for the standard stimuli.

So the aim of this study was to determine unsystematic and systematic variance of the MMN and of the P1 and N1 of the auditory evoked potentials to standard and deviant stimuli in school-age children within (reliability) and between (stability) two experimental sessions. Due to this variability we think it is necessary to determine the reliability of the MMN elicited by different stimulus and deviant types which we plan to use in assessing auditory processing in clinical groups of children. According to the results reported in the literature we hypothesize the best reliability for the MMN elicited by a duration deviant.

Since we often observed two negative components in the difference waveforms, another aim of our experiment was to determine the reliability of this second negative component in comparison to the early MMN. In addition to the typical MMN, e.g. Korpilahti (1996) described a second, later negative component in the difference waveform elicited by speech stimuli which they called 'late' MMN. This negativity might be associated with a 'sensitization process', an automatic preparation for detecting possible subsequent stimulus changes (Alho, 1995). So far, nothing is known about the reliability and stability of this phenomenon.

2. Materials and methods

2.1. Subjects

Fifteen healthy children (8 girls and 7 boys) between 7 and 11 years (mean age = 8.4 years, SD = 1.2 years) were tested twice in a 2 week period. All children had normal hearing thresholds and at least average non-verbal intelligence (i.e. IQ > 85, mean Non-Verbal IQ in the Kaufman Assessment Battery for Children = 106.5, SD = 11.2). We screened subjects for psychiatric symptoms, developmental and neurological disorders by the Child Behavior Checklist (CBCL, Arbeitsgruppe Deutsche Child Behavior Checklist, 1993) and a parent interview. Children whose parents reported a history of language or learning problems or dylexia were also excluded from the study.

2.2. Stimuli and experimental procedures

The experiment consisted of 4 blocks of tones and 4 blocks of speech-stimuli in a balanced order, each containing 333 stimuli with a constant SOA of 1 s. The standard tone (1000 Hz, 175 ms, rise and fall time 10 ms) was replaced by a frequency deviant (1200 Hz, 175 ms) in 15% of the trials and in another 15% by a duration deviant (1000 Hz, 100 ms). The speech stimuli consisted of digitized consonant-vowel syllables of 175 ms duration. They were produced by a female German speaker. The standard phoneme was /da/, the deviants /ga/ and /ba/ varied in place of articulation (Pompino-Marschall, 1995). The stimuli were presented to the right ear via insert earphones with 86 dB SPL intensity. During the recording session children watched a silent video-tape and were instructed to ignore the stimuli. An additional two-alternatives forced choice task was run at the end of the session to test the discriminability of the stimuli. Thereby the mean percentage of correct judgements (hits and correct rejections) as a measure of accuracy of behavioral discrimination was determined. P(c) was clearly above chance level for all stimuli: $p(c)_{\text{frequency}} = 97.9$, SD = 3.8; $p(c)_{\text{duration}} = 90.8$, SD = 9.4; $p(c)_{/\text{ba}/} = 97.0$, SD = 5.2, $p(c)_{/\text{ga}/} = 92.6$, SD = 10.5.

2.3. EEG recording and data analysis

Silver-chloride electrodes were attached according to the international 10–20 system. Reliability and stability of the MMN were determined on basis of the data measured at three frontal (Fz, F3, F4) and three central (Cz, C3, C4) electrode sites. The electrodes were referenced to averaged mastoids. Two additional pairs of electrodes were used to detect horizontal and vertical eye movements.

Data were acquired using the *Neuroscan* system at a sampling rate of 256 Hz. On-line bandpass filtering was set to 0.1–30 Hz and signals were stored for off-line analysis. The time epoch for analysis consisted of 800 ms after stimulus onset and a 200 ms prestimulus baseline against which amplitude measurements were made. Off-line processing included artifact rejection of epochs containing significant EOG-signals and EEG-activity exceeding $\pm$ 80 μV and averaging of epochs. The mismatch negativity was obtained by subtracting standard and deviant evoked responses for each deviant type. For visual evalutation of the MMN we used a 3 category rating scale (present, questionable, absent) as described by Kurtzberg et al. (1995). A MMN was considered to be present if the difference waveform showed a negative deflection exceeding background activity in amplitude in the latency range of the grand mean (grand mean peak $\pm$ 100 ms). If the amplitude was not higher than the amplitudes of background activity or the negative peak occurred not in the latency range of the grand mean it was rated as questionable. If none of the criteria were fulfilled the MMN was rated as absent.

From the difference waves mean amplitudes for 100 ms-time windows around the peaks of the group grand-averages of each stimulus condition were calculated. The components P1 and N1 were identified visually as the first positive and first negative deflection of the individual standard and deviant waveforms.

Reliability within sessions (odd-even-method) and stability between sessions was determined by Pearson's correlations of the ERP-amplitudes and latencies. Spearman–Brown correction for test length was used for the calculation of the reliability coefficients.

3. Results

The data of one girl were excluded because of excessive eye artifacts. In accord with Korpilahti and Lang (1994) and others we observed two negative peaks of the difference waveforms in many individual averages of both stimulus types and in the group averages of the tone conditions (Fig. 1A,B). The grand-average waveforms of the speech stimuli conditions show a broader negativity (Fig. 1C,D).

3.1. Visual rating

Table 1 shows the results of the visual rating of the mismatch negativity. All deviant types could elicit a clear MMN in a considerable number of children in at least one of the sessions (see line 3 of Table 1). A stable rating 'present' in both sessions was observed for the early MMN and the later negativity to the duration deviant in seven children (50%). The frequency deviant elicited a stable early MMN in 5 (36%) and a late negativity in 10 (71%) children. To both speech deviants (/ba/ and /ga/) the MMN response was stable across sessions (rated as 'present') in 6 (43%) children. A stable rating 'absent' or 'questionable' occurred only in a few cases, while 4–7 children showed a clear MMN in only one of the two sessions. The correlation of the three category rating between the two sessions (contingency coefficient) did not reach significance for any of the deviant types and time ranges. It only showed a tendency to significance for the deviant syllable /ga/ ($P = 0.06$) and the early time window for the frequency deviant ($P = 0.09$).

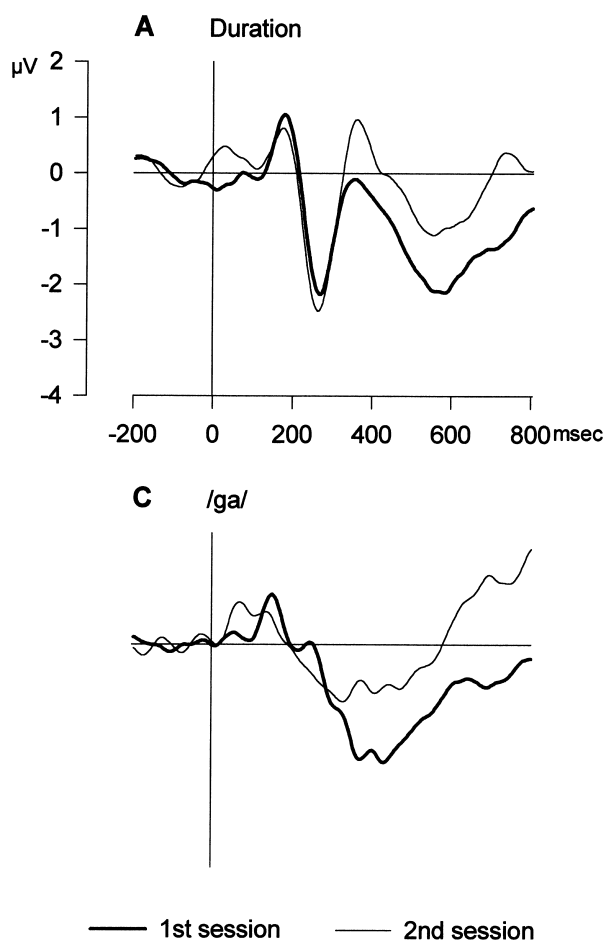

Fig. 1. MMN waves at Fz elicited by the duration (A) and frequency (B) deviant (top) and the syllables /ga/ (C) and /ba/ (D); grand-average ERPs of the two sessions are superimposed.

Table 1
Frequency of the MMN rated as 'present' in 14 subjects

	Tones				Syllables	
	Frequency		Duration		GA	BA
	100–300	350–550	160–360	460–660	360–560	360–560
Session 1	8	12	10	11	12	9
Session 2	7	12	10	8	7	8
Session 1 or/and Session 2	10	14	13	12	13	11
Session 1 and Session 2 (stable rating)	5	10	7	7	6	6

Comparisons of subgroups of children with stable vs. unstable MMN revealed no significant differences regarding the variables age, non-verbal intelligence, performance in the discrimination task and gender (*t*-tests for independent samples).

3.2. Reliability of MMN parameters within sessions

Table 2 shows the within-session reliability of mean amplitudes separately for the two test sessions for the electrodes Fz and Cz. During the first test session correlation coefficients reached significance only for the frequency deviant at Fz and for the duration deviant at the central electrodes (Cz). During the second session the highest correlations were reached for the frequency deviant at Fz in the first time window, for the duration deviant at Cz also in the early time window and at Fz in the second time window and for the syllable /ga/ at Fz. The coefficients varied considerably across electrodes, stimulus conditions and sessions, but significant correlations were all positive except for the second time window during the second test session for tone stimuli. Responses to the speech-stimuli appeared generally less reliable than those to the tone stimuli.

3.3. Overall stability of the MMN

A repeated measures ANOVA (factors: test session, electrode and stimulus condition) revealed no significant differences between the electrodes ($F(5,70)$, $\varepsilon = 0.49$, n.s.). The mean amplitudes (Table 3) were significantly lower in the second session ($F(1,14) = 10.39$, $P = 0.006$), but the effect of repetition differed between the stimulus conditions (interaction test session × stimulus type: $F(3,42) = 4.16$, $\varepsilon = 0.72$, $P = 0.023$). Separate analyses showed that the differences between the experimental sessions were mainly due to the decrease of the mean amplitudes in the speech condition (syllable /ga/: $F(1,14) = 5.47$, $P = 0.035$; syllable /ba/: $F(1,14) = 11.32$, $P = 0.005$, see also Fig. 1C,D). Since the grand-mean over both test sessions showed a second peak only for the tone stimuli, mean amplitudes in a second time window were calculated only for these conditions (Table 3). They showed a significant effect of test repetition for the frequency deviant ($F(1,14) = 19.39$, $P = 0.001$) but not for the duration deviant ($F(1,14) = 0.72$, n.s.; compare also Fig. 1A,B).

3.4. Individual stability of the MMN between sessions

Significant test-retest correlations (Table 2) were found for the duration deviant at the electrodes Fz and for the speech deviant /ga/ at the electrode Cz. The responses to speech stimuli showed moderate stability, while the lowest correlations were found for the frequency deviants. The amplitudes in the second time window were unstable with no significant correlations.

Table 2
Split-half-reliability (Pearson's *r*, Spearman–Brown corrected) and retest-stability (Pearson's *r*) of mean amplitudes

		Tones				Syllables	
		Frequency		Duration		GA	BA
		150–250 ms	400–500 ms	210–310 ms	510–610 ms	410–510 ms	410–510 ms
Split-half-reliability							
Session 1	Fz	0.60 *	0.46*	0.36	0.44	0.18	−0.33
	Cz	0.15	0.37	0.78**	0.49*	−0.15	0.04
Session 2	Fz	0.57*	−0.08	0.34	0.60*	0.63**	−0.45
	Cz	−0.34	−0.55*	0.79**	−0.52*	−0.13	0.18
Retest-stability							
	Fz	0.12	0.45	0.55*	−0.33	0.36	0.35
	Cz	0.20	0.43	0.51	−0.24	0.60*	0.30

Table 3
Mean amplitudes (Fz) in μV (± SD) ($n = 14$)

	Tones				Syllables	
	Frequency		Duration		GA	BA
	150–250 ms	400–500 ms	210–310 ms	510–610 ms	410–510 ms	410–510 ms
Session 1	−1.8 (±1.6)	−3.3 (±1.5)	−1.9 (±1.8)	−2.2 (±2.2)	−2.8 (±1.8)	−2.1 (±2.1)
Session 2	−1.1 (±1.7)	−1.2 (±1.6)	−2.5 (±1.8)	−1.4 (±1.6)	−1.0 (±1.6)	−1.2 (±1.3)

3.5. Stability and reliability of P1 and N1

The grand average ERPs (Fig. 2) show a positive peak around 100 ms (P1) followed by a negative component around 250 ms of much higher amplitude. This structure is typical for young school-aged children (Courchesne, 1990).

Table 4 shows means and standard deviations of the amplitudes of these components. The effects of the factors test session and stimulus type were determined by repeated measures ANOVAs separately for the standard and deviant P1 and N1. These analyses showed a significant difference between the test sessions for the standard N1 ($F(1, 13) = 11.66$, $P = 0.005$) as well as the N1 in the deviant response ($F(1, 13) = 15.79$, $P = 0.002$). The P1 standard amplitudes were also significantly attenuated during the second session ($F(1, 12) = 10.10$, $P = 0.008$). For the P1 deviant amplitudes, however, there was no significant difference between the experimental sessions. The factor stimulus type (tone vs. speech stimuli for the standards; levels frequency, duration, /ba/, /ga/ for the deviant stimuli) had no significant effect on the N1 and P1 amplitudes.

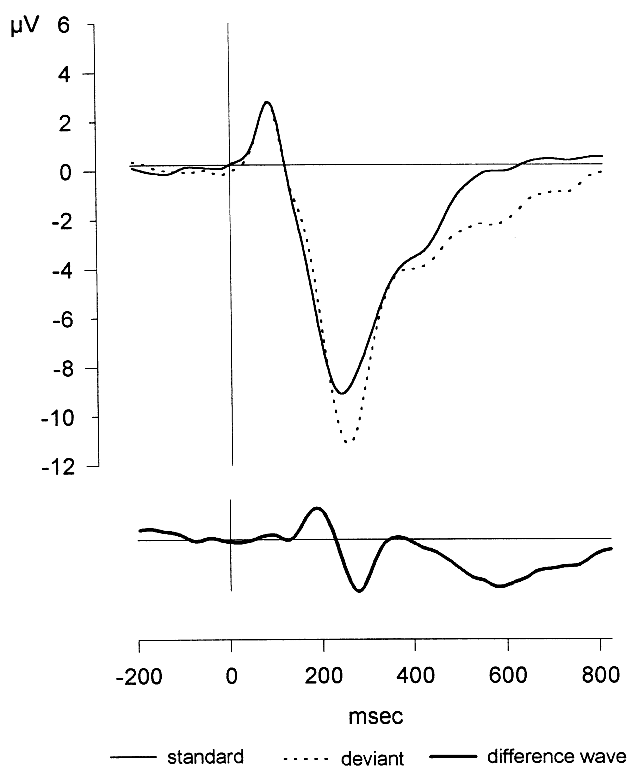

Fig. 2. Standard, deviant (top) and difference waveform (bottom) to the duration deviant during the first experimental session.

Table 5 shows split-half reliabilities of the P1 and N1 amplitudes for the first test session and retest stabilities between sessions. The split-half reliability of the P1 and N1 amplitudes was clearly better than for the MMN, especially for the standard responses. The results were similar for the second session. The individual retest stability across the two experimental sessions was high for both components, but was somewhat higher for the N1. Almost all correlations between the amplitudes of the two sessions were significant. In general, the peaks of the standards showed a better stability than those of the deviant waveforms probably due to the larger number of sweeps.

4. Discussion

4.1. ERP measures

The MMN is a useful tool for studying the function of sensory memory and automatic auditory discrimination in groups of patients as shown for instance by Korpilahti and Lang (1994) in language impaired children, by Kraus et al. (1996) in learning disabled children or by Ponton and Don (1995) in cochlear implant users. Whether it has a predictive value in children at risk for reading disorders (Csépe et al., 1997; Leppänen and Lyytinen, 1997) or language disorders (Cheour et al., 1997) is under study.

In the present study, the reliability and stability of MMN parameters was generally not sufficient to allow the application of the MMN as an individual diagnostic measure. Compared to the results obtained in adults in a similar experiment (Uwer and von Suchodoletz, 1998) the split-half and the retest-reliability in children was lower. This might be due to the slower and less regular EEG background activity in children that causes an unfavorable signal-to-noise ratio (SNR).

The age span of our study group was too large to rule out the hypothesis that maturational changes might account for a high interindividual variability (Table 3), but in our data there was no significant correlation between age and performance in the discrimination tasks as well as between age

Table 4
Peak amplitudes of the ERP-components P1 and N1 at Fz in μV and ms (± SD), respectively, and number of averaged epochs

		Tones			Syllables		
		Standard	Frequency deviant	Duration deviant	Standard	Deviant 'Ga'	Deviant 'Ba'
P1	Session 1	4.2 (±1.4)	4.3 (±1.9)	4.5 (±2.1)	3.7 (±2.0)	3.8 (±2.0)	3.9 (±2.3)
	Session 2	3.5 (±1.5)	3.4 (±1.6)	3.6 (±1.8)	2.9 (±1.7)	3.6 (±2.3)	3.3 (±2.1)
N1	Session 1	−6.7 (±4.6)	−9.3 (±5.4)	−8.4 (±4.5)	−7.4 (±3.4)	−8.9 (±4.2)	−9.4 (±3.3)
	Session 2	−5.7 (±3.3)	−7.7 (±4.2)	−5.4 (±6.6)	−5.8 (±2.4)	−7.0 (±3.4)	−6.6 (±3.4)
Number of sweeps							
	Session 1	701 (±115)	151 (±20)	148 (±27)	664 (±157)	143 (±30)	143 (±35)
	Session 2	745 (±59)	159 (±17)	160 (±15)	748 (±90)	158 (±18)	161 (±20)

and MMN amplitudes or MMN ratings. Csépe et al. (1997) observed no changes of phonetic sensitivity (measured by the MMN) to place of articulation contrasts between the age of six and ten, but a large variability of the MMN to voicing contrasts in younger children (6–7 years). In a study by Elliott et al. (1981) 10 year old children performed significantly better on a labeling task with natural speech sounds contrasting in place of articulation than 6 year olds. So, further research is needed to clarify the maturation of phonetic sensitivity measured by behavioral tasks on the one hand and ERP-measures like the MMN on the other hand. But the rather low intraindividual stability between two experimental sessions cannot be accounted for by maturational changes. In our data the stability of the MMN did not vary with age, non-verbal intelligence, discrimination performance or gender.

In accordance to the studies of Pekkonen et al. (1995) and Kathmann et al. (1999), a duration deviant elicited a more stable MMN than a frequency deviant or speech stimuli. The stability coefficients found in these studies in adults were higher than those in our study in children but varied across stimulus types and electrode sites. In general, they were still below the level that would be expected of a reliable diagnostic tool. Therefore results of a single test session in an individual patient should be interpreted very cautiously and it seems premature to base diagnostic or therapeutic decisions on them. This might be the case when MMN is used for intraoperative monitoring in epileptic patients as it has been proposed by Liasis et al. (1997).

The so called 'late' MMN occurring more than 400 ms after stimulus onset was even less stable than the MMN within the typical time window around 200 ms. Although it is often observed in individual responses and also in grand averages it does not offer a more reliable correlate of automatic discrimination, at least in children.

It has been emphasized by different authors (Kurtzberg et al., 1995; Lang et al., 1995; McGee et al., 1997) that it is necessary to improve the SNR of the MMN in order to reach a sufficient reliability. So far the usual way to do this is to enlarge the number of deviants that are averaged. However, the possibility to apply this method is very limited in children. Let alone practical problems, Lang et al. (1995) observed that MMN amplitudes decreased during longer experimental sessions in young adults. Other methods, e.g. selecting sweeps with better SNR (see Kurtzberg et al., 1995) have been proposed but are not yet generally accepted for use in the clinical routine.

Since the MMN is a difference measure, a low reliability of the acoustic evoked responses to the standard and the deviant stimuli might be an explanation for its high variability. The components P1 and N1 of the standard and deviant responses, however, showed a good reliability and replicability especially for the standard responses reaching similar levels as described for adults (Pekkonen et al., 1995; Escera and Grau, 1996). In contrast to the results found by Escera and Grau (1996), in our data the replicability of the N1 amplitudes was also much higher in the deviant responses than the individual stability of the MMN ampli-

Table 5
Split-half-reliability (Pearson's *r*, Spearman–Brown corrected) and retest-stability (Pearson's *r*) of P1 and N1 amplitudes at Fz

	Tones			Syllables		
	Standard	Frequency deviant	Duration deviant	Standard	Deviant 'Ga'	Deviant 'Ba'
Split-half-reliability session 1						
P1	0.80**	0.28	0.68*	0.84***	0.66**	0.80**
N1	0.84**	0.87**	0.56*	0.94***	0.57*	0.74**
Retest-stability between sessions						
P1	0.58*	0.10	0.79**	0.84***	0.61*	0.52
N1	0.90***	0.82***	0.70**	0.83***	0.74**	0.76**

tudes. Source analyses of the ERPs of this study (Albrecht et al., 1998) showed very stable results for the N1 as well and a low stability for the MMN sources. The somewhat lower reliability of the deviant responses as compared to the standards is probably due to the fact that for these waveforms a lower number of sweeps were averaged resulting in a lower SNR. The low reliability and stability of the MMN in our data can, therefore, not mainly be attributed to the low reliability of the evoked responses in the data in general. It rather seems that here is some variability in the MMN itself.

4.2. Visual inspection

Each of the four deviant stimuli used in this study elicited a MMN in at least 71% of the children in one of the two test sessions according to visual inspection. The stability of this rating was low though for all deviant types. McGee et al. (1997) found a high rate of false positive decisions when they identified MMNs to speech stimuli in children by visual inspection. They determined the validity of the yes/no decisions by rating the difference waveforms between standards and deviants and between two deviant responses. In this latter condition there was no acoustical difference between the stimuli, thus differences in the responses were only due to physiological noise. 64% of these difference waveforms were erroneously rated as MMNs. While we used a different access to the problem by testing the stability of this decision, our data lead to a similar conclusion regarding the visual rating. The presence of a MMN in an individual child cannot be assessed with enough certainty by rating the difference waves of a single test session.

4.3. Conclusions

The MMN has been repeatedly proven to be useful in the study of automatic auditory perception in groups of children. The reliability of this measure, however, is low in certain conditions and so far not sufficient for the use in individual cases. A duration deviant seems to elicit the most stable MMN in children and adults. The reliability of speech stimuli, which might be more interesting in some clinical applications, e.g. with language-impaired children, reached about the same level as the MMN elicited by the frequency deviant.

With the high level of unsystematic variance in the MMN responses, samples must be relatively large to allow for statistically significant differences between normal controls and groups of patients even if the differences in the grand means appear to be clear.

A small age span of the experimental group would help to avoid a confoundation of group differences and differences due to developmental changes of the phonetic sensitivity that can be observed still in early school age.

Recently several new methods to assess the presence of a MMN in individual averages were proposed. McGee et al. (1997) compared different criteria for the presence of a MMN which were based on the measurement of latency, amplitude, duration and area by using signal detection theory techniques. Ponton et al. (1997) suggested the use of the so called integrated mismatch negativity, a noise-free measure that allows to calculate the exact probability of the presence or absence of a MMN. These new methods could improve the qualitative decision whether a person shows a MMN to certain stimuli or not. Whether the results obtained by these methods would be stable over a certain time interval, however, remains to be tested.

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