

Detecting violations of temporal regularities 1

Detecting Violations of Temporal Regularities in Waking and Sleeping Two-month-old Infants

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Abstract

Correctly processing rapid sequences of sounds is essential for developmental milestones, such as language acquisition. We investigated the sensitivity of two-month-old infants to violations of a temporal regularity, by recording event-related brain potentials (ERP) in an auditory oddball paradigm from 36 waking and 40 sleeping infants. Standard tones were presented at a regular 300 ms inter-stimulus interval (ISI). One deviant, otherwise identical to the standard, was preceded by a 100 ms ISI. Two other deviants, presented with the standard ISI, differed from the standard in their spectral makeup. We found significant differences between ERP responses elicited by the standard and each of the deviant sounds. The results suggest that the ability to extract both temporal and spectral regularities from a sound sequence is already functional within the first few months of life. The scalp distribution of all three deviant-stimulus responses was influenced by the infants' state of alertness.

Keywords: Infants; Event-related potential (ERP); Mismatch Negativity (MMN); auditory oddball paradigm; ISI-deviant stimulus; State of Alertness

Introduction

The perception and representation of timing in the human brain has been fascinating researchers for a long time. Temporal processes have been separated into different time scales from circadian rhythms to processes in the millisecond range (Mauk and Buonomano, 2004) and numerous studies were carried out to gain insight into mechanisms underlying temporal processing in the brain (e.g. Mauk and Buonomano, 2004; Ivry and Spencer, 2004; Lewis and Miall, 2009; Koch et al., 2009). Most studies into the subject have been conducted on adults and pre-school and school-age children. Less is known, however, about the temporal processing abilities of infants. Extending our knowledge about these processes is fundamental for understanding developmental milestones, such as language acquisition, in which temporal processes play an important role. For example, in some languages phoneme duration may distinguish between minimal pairs of words (Peterson and Lehiste, 1960). Also, several studies showed that the ability to accurately process the temporal characteristics of rapidly presented sequences of sounds is critical for analysing and segmenting spoken language (Tallal et al., 1985; Benasich and Leevers, 2002; Fitch et al., 2001; Benasich et al., 2006). Therefore, the aim of the current study was to test whether infants are sensitive to violations of temporal regularities, i.e. to unpredictable changes in the timing of auditory stimulus delivery.

Using cardiac responses and behavioural measures, it has been shown that infants are sensitive to some temporal stimulus parameters and have a degree of control over timing their actions. For example, Pouthas and colleagues (1996) found that newborns and two-month-olds could learn to time pauses between non-nutritive sucks. Jusczyk et al. (1983) and Eilers et al. (1984) obtained evidence showing that two-month-old infants accurately discriminated sounds that differed by a few hundred milliseconds in duration. In five-month-old infants, Chang and Trehub (1977) demonstrated discrimination between multi-tone patterns of identical tonal components but different temporal arrangements of the tones.

Studies using electrophysiological methods have also provided insights into stimulus processing in infants. A number of these studies measured infant analogues (Alho et al., 1990) of the mismatch negativity (MMN; Näätänen et al., 1978) event-related brain potential (ERP). The MMN is a cortical response to deviations from the regular features of a sound sequence (for a recent review, see Näätänen et al., 2011) and it has been suggested to reflect processes evoked by failed auditory predictions (Winkler, 2007). The MMN is most often studied in the auditory oddball paradigm, in which a repeating sound is occasionally exchanged for a different sound. However, violations of complex regularities can also evoke the MMN (Näätänen et al., 2001).

The MMN component has been extensively studied in adults. Relevant for the current study are the MMN results regarding the detection of violations of temporal regularities. The MMN has been elicited by occasional decreases and increases in stimulus duration (Näätänen et al. 1989; Winkler et al., 1996), shortenings of the stimulus onset asynchrony (SOA; onset-to-onset interval) and the inter-stimulus interval (ISI; offset-to-onset interval; Nordby et al., 1988; Takegata et al., 2001), stimulus omissions (Yabe et al., 1997), and infrequent changes in the temporal structure of complex sounds (Grimm and Schröger, 2005; Winkler et al., 1998) and sound patterns (Müller and Schröger, 2007; Takegata et al., 2005; Winkler and Schröger, 1995). These studies provided evidence that the various temporal aspects of auditory stimulation are encoded in the memory underlying the MMN response and that the MMN is elicited by violations of temporal expectations (for a review, see Czigler et al., 2003).

MMN experiments are quite suitable for infant studies, because, in contrast to most other ERP components, MMN-like discriminative ERP responses ('mismatch responses'; MMRs) can be obtained very early in infancy (Cheour, 2007), they require no behavioural response (Nelson and Bloom, 1997), and are elicited by unattended stimuli also (Sussman, 2007). Furthermore, the component can be recorded in waking as well as in sleeping infants (Kushnerenko et al., 2001a), although mixed results have been found as to whether or not

the infant's state of alertness influences the MMR (see for example Friederici et al., 2002; Hirasawa et al., 2002; Cheour et al., 1998).

Despite the advantages, only a relatively small number of MMN experiments tested violations of temporal regularities in infants. Kushnerenko et al. (2001b) showed that infants aged 2-6 days are sensitive to increases in tone duration, evident in changes in their N2 responses. Also, Kushnerenko et al. (2001a) found that neonates are able to discriminate duration changes in speech sounds, demonstrated by a negative inflection in their ERP wave. Winkler et al. (2009b) obtained an MMR to violations at the downbeat of a rhythmic sound pattern in newborn infants. Finally, results from an experiment by Brannon et al. (2004) suggested that ten-month-old infants can accurately detect changes of a temporal interval within a sequence of tones.

These studies showed that infants and even neonates have some sense of timing and they react to temporal deviations with a discriminative response comparable to the adult MMN. The goal of the current study was to shed light on whether infants can identify violations of temporal regularities in a repetitive auditory sound sequence, by testing whether they detect occasional shortenings of the otherwise uniform ISI. In addition, since some studies suggested that the MMR may vary as a function of the infant's state of alertness (Friederici et al, 2002) and approximately half of the infants were asleep during the EEG recording, the effects of the state of alertness on the MMR were examined by comparing the ERP responses between waking and sleeping infants. The stimulus paradigm, developed for our ongoing longitudinal study, was adapted from the one designed by Kushnerenko et al. (2007), adding ISI deviants to the rare environmental (contextually novel) and white noise sounds (high spectral deviance) embedded in a regular sequence of a repetitive complex tone. The effects of the infants' state of alertness on the responses to the rare environmental and white noise sounds will also be presented.

Methods

Subjects

Subjects were 76 infants whose mothers have been taking part in a longitudinal study on prenatal early life stress (PELS project). The study was approved of by the Medical Ethical Committee of St. Elisabeth Hospital in Tilburg, The Netherlands. Informed consent was obtained from all mothers and fathers in accordance with the Declaration of Helsinki.

For the PELS project, a total of 190 pregnant women had been recruited, of whom 178 before their 15th and 12 between their 15th and 23rd week of pregnancy. Recruitment took place at a general hospital and four midwives' practices in and around Tilburg, The Netherlands. Pregnancies were dated using crown-rump length (CRL) around the 12th week of pregnancy measured by a professional, or the last menstrual period when CRL data were unavailable. The women were followed up during their pregnancies and were invited for postnatal observations either two or four months after the birth of their babies. Ninety-one women visited the lab for testing when their babies (54 girls) were aged two months and of these recordings, data from 76 infants (46 girls) were suitable for analysis. Data from 15 infants were excluded from the analyses due to crying (2), excessive movements/artifacts (9), and technical problems (4). The mean age of the remaining infants at testing was 9.6 weeks (M=70.1 days, SD=6.2 days). Mean gestational age and mean birth weight were 39.9 weeks (SD=10.5 days) and 3454 g (SD=474 g), respectively. All infants were healthy and had passed a screening test for hearing impairments, performed by a nurse from the infant health care clinic, between the 4th and 7th day after birth. During testing in our lab 36 of the infants were awake (20 girls) and 40 were asleep (26 girls).

Stimuli

The stimulus sequences consisted of 4 types of tones - one standard and three deviants - each with 10 ms rise and fall times and of 200 ms duration. Stimuli had an intensity level of 75 dB and were delivered at a uniform 300 ms ISI (offset-to-onset), except for the ISI-deviant events (see below). The standard sound was presented at a probability of 0.7 and the three types of deviants with a probability of 0.1, each. The standard was a complex tone constructed from the 3 lowest partials. The fundamental frequency was 500 Hz and the

intensity of the second and third partials was 6 and 12 dB lower, respectively, than that of the first one. One deviant was identical to the standard sound, but preceded by 100 ms instead of 300 ms ISI ('ISI-deviant'). The other two deviant types (spectral deviants) were white noise segments ('white noise sound') and environmental sounds ('novel sounds', 150 different ones), such as a barking dog and a door bell. Each novel sound was delivered only once during the experiment to maintain novelty throughout.

Sounds were presented in a semi-random order with the restriction that both white noise and novel sounds were always preceded by at least two standard sounds or a combination of a standard sound and an ISI-deviant. Also, consecutive ISI-deviants were always separated from each other by at least two standards or by a standard combined with either a white noise or novel sound. In total, 1150 standard sounds were presented and 150 deviants of each type. The stimuli were divided into five blocks of 300 stimuli, each and presented with short breaks in between. The order within the five stimulus blocks was separately randomized, and their presentation order was counterbalanced across subjects.

Procedure

The infants were tested at the developmental psychology lab at Tilburg University, The Netherlands, in a dimly lit and sound-attenuated room. During the experiment, parents were seated in a chair facing a pair of speakers while holding the infant in their arms. The speakers were placed 60 cm apart, both ca. 80 cm from the baby's head. The parent-child dyad was observed through a pair of camera's and notes were taken on whether the baby was quiet, crying, awake or asleep and whether or not he/she was sucking a pacifier, the parent's finger, a toy, etc. As some authors (e.g. Friederici et al., 2002) found that in infants the MMRs to deviant sounds changed as a function of the state of alertness, we divided our sample into a waking and a sleeping subgroup and state of alertness was later used as a between-subjects factor in the analyses. The monitored behaviour in combination with the online electroencephalography (EEG) signal was used to determine in which state of alertness the baby was during each stimulus block: awake or asleep with active (REM) and

quiet (non-REM) sleep collapsed into a single category. Only data recorded during those stimulus blocks in which the infant was either awake or asleep throughout the whole period were analysed.

Before the start of the experiment, the infants were familiarised with the standard sound, the ISI-deviant and the white noise segments. The novel sounds were not included in this pre-test making sure that they were indeed new to the infants during the actual experiment. The standard sound thus became a 'frequent familiar' stimulus, the white noise sound and the ISI-deviant 'infrequent familiar' and the novel sounds 'infrequent unfamiliar' stimuli (Richards, 2003).

Data acquisition and analysis

The EEG was recorded with Biosemi ActiveTwo amplifiers (www.biosemi.com) with 512 Hz sampling rate using a head cap with 64 electrode locations placed according to the revised version of the International 10-20 system. Two reference electrodes were placed on the left and right mastoids, respectively.

Off-line, the EEG signals were filtered with a 1 to 30 Hz band-pass filter (slope 24 dB) and a 50 Hz notch filter and were segmented into 600 ms epochs, including a 100 ms pre-stimulus interval as the baseline. The epochs were averaged separately for each deviant stimulus type, excluding epochs with sample-to-sample voltage steps larger than 100 μV or in which the amplitude range exceeded 120 μV in a sliding window of 200 ms anywhere within the whole epoch. Data from infants with less than 40 acceptable responses for any one of the three deviants were removed from further analysis (9 infants). Difference waveforms were calculated by subtracting the response to the standard sound separately from the response elicited by the ISI-deviant, the white noise sound, and the novel sound.

As the MMR was expected to be localised mostly over frontal (F3,Fz,F4) and central (C3,Cz,C4) electrode sites, for each deviant sound type, the grand-averaged difference waveforms were averaged together from these areas for locating the MMR responses separately for the three deviants. Although the overall morphology of the deviance-related

ERP responses was compatible with that found by Kushnerenko and colleagues (2007), there were large latency differences between the three types of deviants. The most prominent response was a broad positive-going difference waveform which was measured between 410 and 470 ms for the ISI-deviants, 385 and 445 ms for the white noise sounds and 275 and 335 ms for the novel sounds. An earlier negative-going difference waveform could also be observed in the ISI-deviant response with similar, although less pronounced deflections discernible for the other two deviants. However, the absolute voltage values of these responses were mostly positive.¹ Therefore, for assessing the amplitudes of these negative-going waveforms, we subtracted the mean voltage in the 20 ms window at the start of the waveform (centred on the preceding positive-going peak) from the mean voltage in the 20 ms window centred on its peak. Short windows were used because the reference positive-going peaks were typically quite narrow and thus symmetric measurements required both windows to be short. For the ISI-deviant, an onset window of 65-85 ms and a peak window of 215-235 ms were used. For the white noise sounds, these windows were 156-176 ms and 187-207 ms, respectively, and for the novel sound, 185-205 ms and 207-227 ms windows were used.

Elicitation of the difference responses (the MMRs) was tested by comparing the mean frontal (F3,Fz,F4) amplitude of each deviant's difference wave in each measurement interval to zero using two-tailed Student's *t* tests, separately for the two states of alertness (2 states of alertness x 3 deviants x 2 measurement intervals = 2 x 6 *t* tests). Holm-Bonferroni (Holm, 1979) correction was used to control for increases in Type I errors due to multiple comparisons. Then, for testing the effects of the state of alertness on the amplitude and scalp distribution of the deviant-minus-standard difference responses over sites F3, Fz, F4,

¹ Note that the ERP effects of the preceding standard stimulus are shifted by 200 ms for the ISI deviants. This misalignment is probably responsible for the positive waveform at $t=0$ as well as positive shift reducing the absolute (negative) amplitude values. However, because the standard-stimulus response is mainly flat by 500 ms post-stimulus, this does not substantially bias the peak-to-peak measurements of components, as they were measured from latency ranges past 500 ms from the onset of the preceding standard stimulus.

C3, Cz, C4, P3, Pz and P4, ANOVAs were run with 'Deviant Type' (ISI-deviant, white noise sound, novel sound) x 'Anterior vs. Posterior' (frontal, central, parietal) x 'Laterality' (left, medial, right) as within-subjects factors and 'State of Alertness' (awake vs. asleep) as a between-subjects factor, separately for the two measurement intervals. Greenhouse-Geisser correction was used where applicable and the ϵ correction factor given, together with the partial η^2 effect size when describing the results.

Results

Figures 1 and 2 present the grand-averaged difference waveforms (frontal, central, and parietal sites) for the three types of deviants in waking and sleeping infants, respectively. Grand-averaged waveforms in response to the standard sound can also be found in the figures. As was expected on the basis of previous research, the white noise and novel sounds elicited large positive responses. In contrast, the most prominent difference response elicited by the ISI-deviant was a negative-going peak followed by a somewhat smaller late positive-going wave. For all three deviants, the highest-amplitude responses appeared on fronto-central electrode sites. In the sleeping infants the amplitudes seemed to be attenuated compared to those in the waking infants.

These observations are supported by the results of the two-tailed t tests comparing the deviant to the standard responses (see Table 1). Both the white noise and novel sound elicited a significant positive-going MMR, both in the waking and the sleeping infants. Neither of these deviants, however, yielded a significant negative-going response. The ISI-deviant, on the other hand, elicited significant MMRs of both types (positive- and negative-going waveforms), but only in the waking and not in the sleeping infants.

Table 2 summarises the results of the ANOVA for the positive- and negative-going MMRs. Response amplitudes and scalp distributions were significantly different for the ISI-deviant and the novel and white-noise sounds for both MMR responses (main effects of Deviant Type and interactions between Deviant Type and the Anterior vs. Posterior and/or the Laterality factors). There was a significant main effect of the State of Alertness in the

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positive-going MMR and a trend for the same effect in the negative-going MMR. Also, a number of interaction effects between the State of Alertness and the within-subjects factors describing the scalp distribution of the responses have been found, as illustrated by figures 3 and 4. In general, the State of Alertness-related changes in the scalp distributions of the MMR responses were different for the ISI-deviant on the one hand and the white noise and novel sounds on the other. More specifically, for the negative-going MMR, State of Alertness had a larger effect on the response to the ISI-deviant, whereas for the positive-going MMR, State of Alertness had a larger effect on the response to the white noise and novel sounds.

Discussion

The current study tested whether two-month-old infants detect small (200 ms) deviations in the regular inter-stimulus interval in an auditory oddball paradigm with one standard and three deviant sounds. We found significant differences between ERP responses elicited by the standard sound and the ISI-deviant stimulus. This suggests that infants detect even presentation rates and represent them as a regular aspect of the stimulation. Thus adult-like mechanisms for detecting violations in auditory temporal patterns may already be functional in two-month-old infants. This ability is a necessary prerequisite of extracting and representing temporal structure from sound sequences (such as musical rhythm; Winkler et al., 2009b) and, in general, for constructing auditory objects (Winkler et al., 2009a) that span multiple discrete sounds (such as a series of footsteps).

Our results are generally in accordance with the findings of Brannon et al. (2004), who found in ten-month-old infants an early negative deflection at 120-240 ms post-stimulus over frontal brain areas and a late anterior positivity in the ERP difference wave in response to stimuli with deviant onset-to-onset intervals. We also found a negativity in response to our ISI-deviant, most clearly defined in the waking infants, at 215-235 ms from stimulus onset and a late positivity at fronto-central electrode sites. One may speculate that the slightly earlier responses on frontal electrodes found in older infants represent faster temporal analysis due to maturation of the brain (e.g. increased myelination).

As can be seen in figures 1 and 2, the morphology of the responses elicited by the ISI-deviant is quite different from those elicited by the white noise and novel sounds. Whereas the infants responded with a large positive MMR to these latter two deviants, the response to the ISI-deviant is of lower amplitude and - perhaps more importantly - starts with a negative-going discriminative response. This difference was most prominent for the waking infants. In adults, similar findings have been obtained for ISI-deviants. Ford and Hillyard (1981) found that occasionally shortening the ISI between two stimuli in an otherwise isochronous sequence resulted in a large negative waveform peaking 135-220 ms from stimulus-onset. The authors offered two explanations: this response could be unique to stimuli presented earlier than predicted or it could be a manifestation of a more general ERP response to deviance. Nordby et al. (1988), using pitch-deviant and time-deviant tones, concluded that both deviants elicited the MMN and that the differences between the MMNs elicited by these two types of deviants may stem from differences in their discriminability or salience. However, since then, several studies showed that the MMN is not a unitary process; different deviations activate partly separate neural circuits (e.g., Giard et al., 1990), specifically, spectral and temporal deviations result in MMNs with different generator structure (Alain et al., 1999; Takegata et al., 2001). Further, deviance-related responses may appear quite early and may be partly generated subcortically (Grimm et al., in press; Slabu et al., 2010). The same may be true for infants: at least partly different neural circuits may detect stimuli deviating in temporal versus spectral characteristics from a standard sound. However, the infant MMR cannot be regarded as a full equivalent of the adult MMN (see, e.g., Kushnerenko et al., 2007). Therefore, drawing conclusions on the basis of the component structure of the adult MMN may be misleading.

Another difference between the current temporal and the two spectral deviants is that the latter widely deviate from the standard. In adults, these wide deviants are usually termed as "novel" sounds, acknowledging that they usually categorically differ from the standard (context) sounds (Escera et al., 2000; Friedman et al., 2001; Polich, 2007). When presented

amongst tonal standards, sounds with wide distributed spectral contents activate large fresh networks in the auditory system and thus elicit high-amplitude responses, only a part of which can be regarded as being related to deviance detection. This is true both for the adult and infant responses (see, e.g., Kushnerenko et al., 2007). The responses observed in the current study are fully compatible with those previously reported for newborn infants (Kushnerenko et al., 2007). In adults, the P3a component, which is a characteristic part of the novelty response, is thought to be involved in redirecting attention to the incoming stimulus (Escera et al., 2000; Friedman et al., 2001). Although there are speculations as to whether the large positive response observed in infants could be a precursor of the adult P3a, this assumption is difficult to substantiate. Similarly to the deviance-related response, the novelty response in neonates is not a full analogue of the response observed in adults.

The responses obtained in this study were influenced by the infants' state of alertness, although the effect was less dramatic than that found in a previous study (Friederici et al., 2002). In general, for all three deviants we saw smaller responses in sleeping than in waking infants. The state of alertness primarily affected the scalp distribution of the main MMR response for each type of deviance: the negative-going MMR for the ISI and the positive-going MMR for the spectral deviants (white noise and novel sound). It should be noted, however, that our categorisation of the various behavioural states, as allowed by the recording methods and the sample size, may not be sufficiently elaborate for distinguishing between the effects of the various states of alertness (such as quiet sleep, active sleep, drowsy, quiet awake, active awake) on the ERP responses. Pooling together, separately, different sleep and waking states may have distorted some of the effects of the state of alertness. Research focused on the different states of alertness is needed to study these effects in more detail.

As mentioned earlier, the current results support the notion that the perceptual abilities of infants may be somewhat less developed in terms of details, but they are not qualitatively different from that of adults. Therefore, together with similar findings (e.g. Alho et al., 1990;

Cheour-Luhtanen et al., 1996; Cheour et al., 1997; Winkler et al., 2009b) they provide the perceptual basis for many important areas of learning occurring during the first year of life, such as developing the basic means of communication, object representation and motor control. In addition, as our results are based on a rather large group of infants compared to most similar studies conducted previously - thus increasing the reliability of the data - they can potentially be used as normative information for studying typically developing children.

Assessing infants' ability to detect violation of temporal regularities may also be useful for future clinical applications. For example, some studies showed that the amplitude of the MMN-like ERPs elicited by frequency deviance was reduced in newborns and infants with cleft palate. This reduction appeared to remain constant over time (Cheour et al., 1999; Čeponienė et al., 2000). Further, Holopainen, Korpilahti, Juottonen, and Sillanpää (1997) found that the MMN to frequency deviance was attenuated in young children with developmental aphasia. Hence, the MMN/MMR can potentially be used to identify developmental problems such as learning difficulties and speech impairments very early, even before they can be detected behaviourally (e.g. Weber et al., 2005). More research is needed, however, normative as well as clinical, before the MMR component can be used in clinical settings.

The present study investigated whether infants aged two months can discriminate between stimuli which have been presented with different inter-stimulus intervals. Our findings show that they are indeed able to detect deviations as small as 200 ms. These results suggest that the ability to detect violations of temporal regularities develops very early and is already functional within the first few months of life. The distribution of the response to both temporal and spectral deviations is influenced by the state of alertness of the infants.

Conflict of interest

The authors declare that there are no conflicts of interest.

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List of Figures

Figure 1. Group-average (36 waking infants) difference waveforms elicited by the ISI-deviant (solid line), white noise (broken line) and novel sounds (dotted line). Group-average responses to the standard are displayed as a broken-and-dotted line. Stimulus onset is at 0 ms. Amplitude calibration is at the bottom of the figure.

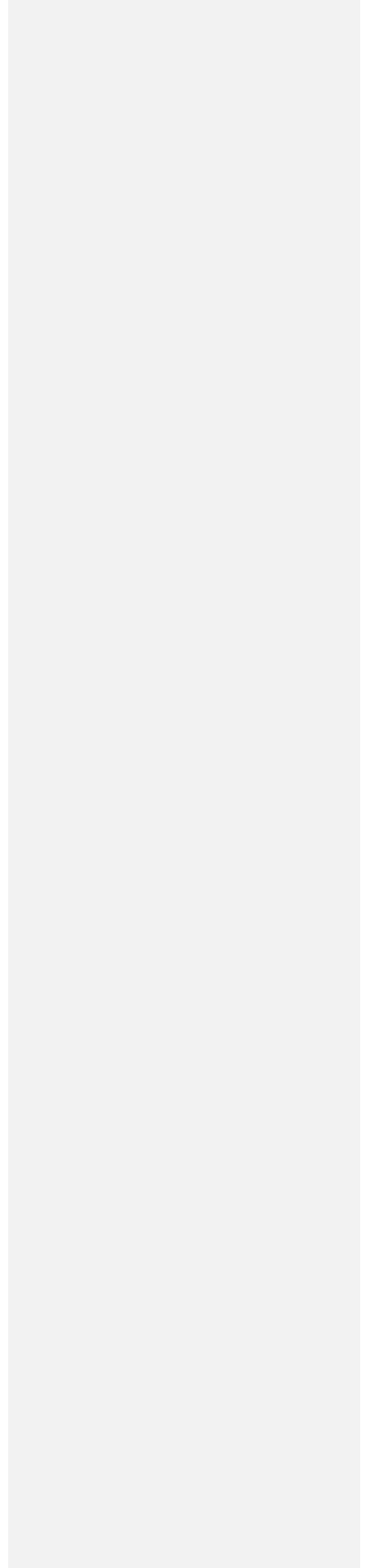
Comment [A2]: Comment 1

Figure 2. Group-average (40 sleeping infants) difference waveforms elicited by the ISI-deviant (solid line), white noise (broken line) and novel sounds (dotted line). Group-average responses to the standard are displayed as a broken-and-dotted line. Stimulus onset is at 0 ms. Amplitude calibration is at the bottom of the figure.

Comment [A3]: Comment 1

Figure 3. Interaction between Deviant Type, Laterality and the State of Alertness for the negative-going MMR. Confidence intervals are included in the figure.

Figure 4. Interaction between Deviant Type, Laterality and the State of Alertness for the positive-going MMR. Confidence intervals are included in the figure.



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Table 1

Results of two-tailed Students' t tests for significant MMRs

State	Negative-going wave				Positive-going wave			
	Awake		Asleep		Awake		Asleep	
	MMR	t(35)	MMR	t(39)	MMR	t(35)	MMR	t(39)
ISI-deviant	-2.14	-3.263**	-1.09	-1.574	1.48	2.656*	.67	1.375
White noise sound	-.08	-.281	.14	.551	6.08	7.009***	3.17	3.882***
Novel sound	.57	3.151 [#]	.49	3.226 [#]	7.96	10.669***	5.12	7.016***

*Note: *p < .05, **p < .01, ***p < .001, [#]only positive significant values were found*

Table 2

Results of omnibus ANOVAs on both negative- and positive-going waves. IWN: Deviant type (ISI-deviant, white noise sound, novel sound), FCP: Anterior vs. Posterior (frontal, central, parietal), LMR: Laterality (left, medial, right).

Source	Negative-going wave					Positive-going wave				
	df	<i>F</i>	<i>p</i>	ϵ	η^2	df	<i>F</i>	<i>p</i>	ϵ	η^2
State of alertness	1,74	3.84	.054 ⁺		.049	1,74	9.89	.002 ^{***}		.118
IWN	2,148	3.90	.044 [*]	.61	.050	2,148	49.74	.000 ^{***}	.93	.402
IWNxState	2,148	1.86	n.s.	.61		2,148	1.30	n.s.	.93	
FCP	2,148	4.50	.021 [*]	.76	.057	2,148	92.55	.000 ^{***}	.76	.556
FCPxState	2,148	1.39	n.s.	.76		2,148	.74	n.s.	.76	
LMR	2,148	17.17	.000 ^{***}	.98	.188	2,148	3.22	.049 [*]	.88	.042
LMRxState	2,148	4.12	.018 [*]	.98	.053	2,148	.39	n.s.	.88	
IWNxFCP	4,296	13.19	.000 ^{***}	.46	.151	4,296	9.01	.000 ^{***}	.75	.109
IWNxFCPxState	4,296	1.08	n.s.	.46		4,296	3.27	.022 [*]	.75	.042
IWNxLMR	4,296	14.78	.000 ^{***}	.67	.167	4,296	5.95	.000 ^{***}	.91	.074
IWNxLMRxState	4,296	4.37	.007 ^{**}	.67	.056	4,296	.33	n.s.	.91	
FCPxLMR	4,296	3.54	.008 [*]	.95	.046	4,296	.57	n.s.	.88	
FCPxLMRxState	4,296	.94	n.s.	.95		4,296	.14	n.s.	.88	
IWNxFCPxLMR	8,592	2.34	.043 [*]	.61	.031	8,592	5.59	.000 ^{***}	.87	.070
IWNxFCPxLMRxState	8,592	1.24	n.s.	.61		8,592	1.56	n.s.	.87	

Note: ⁺*p* < .1, ^{*}*p* < .05, ^{**}*p* < .01, ^{***}*p* < .001, n.s. not significant

Figure 1_for print version

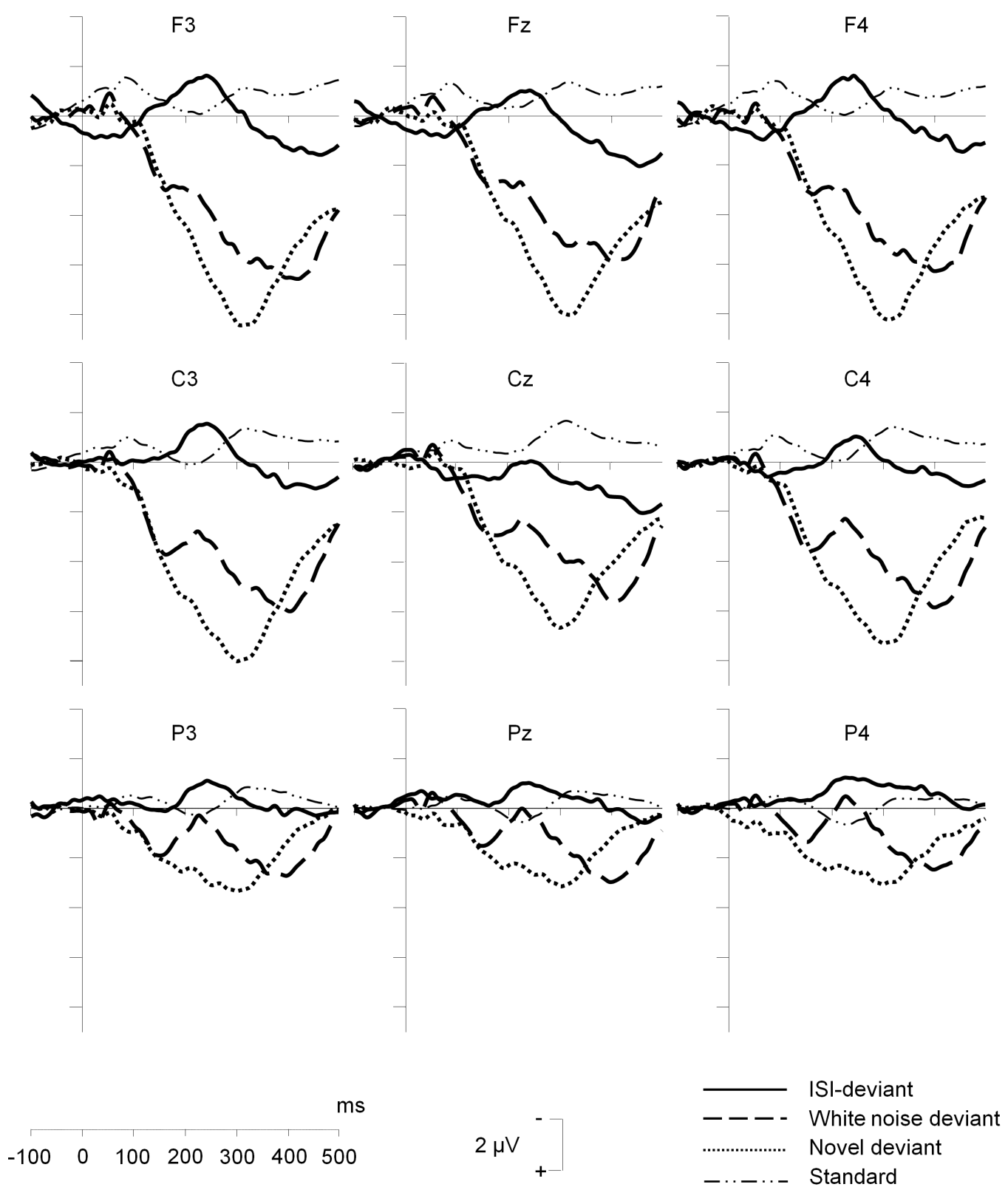


Figure 2_for print version

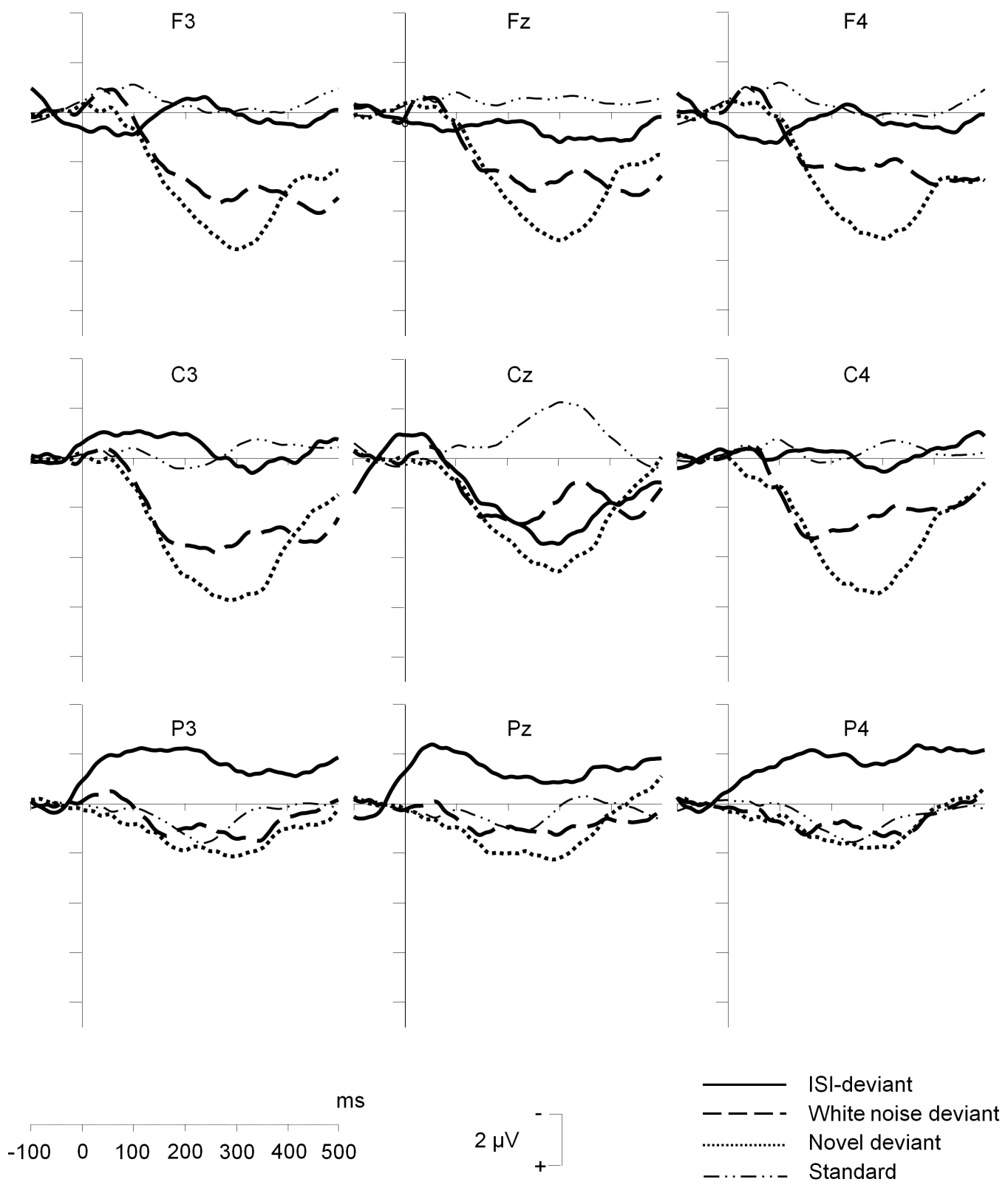


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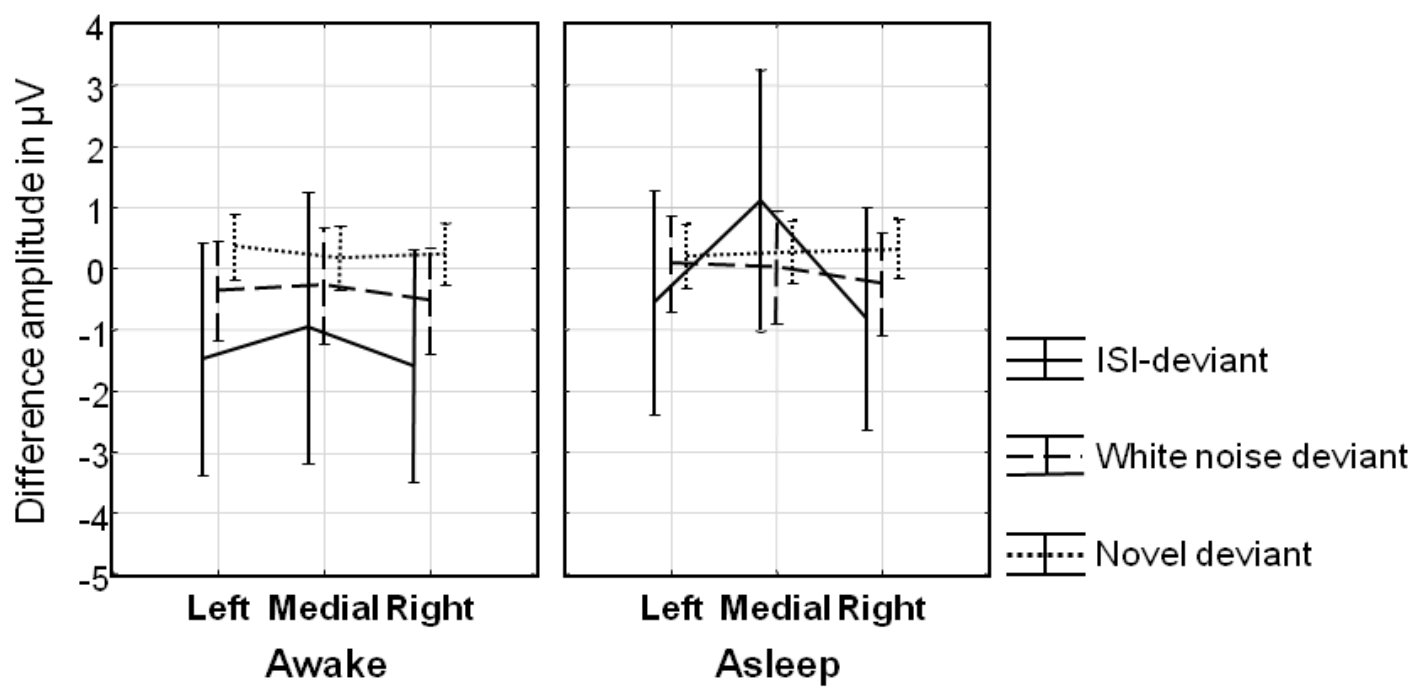


Figure 4_for print version

