Mismatch response is absent in 2-month-old infants at risk for dyslexia

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This study examined auditory processing in 2-month-old infants at genetic risk for dyslexia and in controls. Manipulated natural speech stimuli (/bAk/ and /dAk/), at either side of the phoneme boundary, were presented to these infants and their automatic cortical deviance responses were recorded. Control infants showed two distinct mismatch responses, thus extending similar findings reported with kindergartners in terms of topographical distribution and cortical sources. The absence of such mismatch responses in the infants at risk supports the hypothesis of basic auditory (temporal) processing impairments in the disorder. The results suggest that these early signs of deficient auditory processing may point to problematic categorical perception at a later age. *NeuroReport* 17:351–355 © 2006 Lippincott Williams & Wilkins.

Keywords: Auditory processing, dyslexia, event-related potentials, genetic risk, infants, mismatch negativity

Introduction

Developmental dyslexia runs in families and is a genetically transmitted learning disorder, characterized by severe reading problems but unimpaired intelligence [1]. It is neurobiological in origin, with deficits in the visual and auditory (phonological) domain [2–4], particularly in auditory temporal processing [5] such as phonemic formant transitions [6]. As a result, dyslexic individuals have difficulty in perceiving the differences between stop consonants such as /d/ and /b/ or syllables /da/ and /ba/, as is evident from impaired categorization and discrimination [7,8].

Behavioural studies indicate that categorical perception of phonemes, cued by differences in formant transitions, already occurs in infants [9] but the behavioural techniques used in these infant studies are not well suited for very young infants because they require overt responses and also face some methodological problems. Fortunately, more insight into (cortical) perceptual processing can be reliably obtained by measuring noninvasive event-related brain potentials (ERPs), and a recent review shows that similar auditory (phonological) cortical processing occurs in infants and adults [10]. Nevertheless, there are only a few electrocortical studies on infants with a risk for developing dyslexia (for a recent review, see [11]), although the relevancy of such studies is clear, because they may yield early neurobiological markers of the disorder, which would be advantageous for prediction and (early) intervention. Some of these studies, with newborns or infants, show promising ERP differences or differences between the hemispheric distribution of the brain responses between at-risk infants and controls, and sometimes these responses could be related to later language performance [12,13].

These studies, however, did not directly address the issue of phonemic near-boundary (categorical) perception. It is the purpose of the present ERP mapping study, therefore, to explore (differences in) sensitivity to a phonemic near-boundary contrast (underlying perceptual categorization) in infants at risk for dyslexia and in controls, by employing an odd-ball paradigm designed to elicit mismatch negativity (MMN), which is the brain's response to auditory deviance [14]. Such mismatch responses can also be reliably obtained from infants and newborns [15–17], and even during sleep [18,19].

In the present study, a group of clearly defined infants at genetic risk for dyslexia and a group of control infants were tested at 2 months of age in a mismatch design with natural speech stimuli with spectral changes in the onset frequency of the second formant, yielding a continuum ranging from /bAk/ to /dAk/. From this continuum, two levels were contrasted that have been shown to elicit MMN and that have also been shown to behaviourally differentiate dyslexic individuals from controls [20]. We used topographical analyses of variance and source localization to compare the brain responses from infants at risk and controls.

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Materials and methods

Study participants

The participants were 32 2-month-old infants at genetic risk for dyslexia [12 girls, mean age 8.3 weeks, mean Apgar score (Activity, Pulse, Grimace, Appearance, and Respiration) of 9.3] and 16 control infants (four girls, mean age 8.2 weeks, mean Apgar score of 8.9). These infants were recruited from the Dutch population and were included in the Dutch Prospective Dyslexia Study. Inclusion in the at-risk group was based on (1) a family history of the parents with respect to reading problems and dyslexia and (2) scores of the affected parents, and of an additional first- or second-degree relative of these parents, on a test battery including speed tests on real word reading, nonword decoding and verbal IQ [21]. Dyslexia did not occur in the control group families and both parents had to score above criterion on our dyslexia test. All participating families received oral and written information about the study and all gave informed consent. The study protocol was approved by a medical ethics committee.

Stimuli, paradigm and procedure

Second formant (F2) transitions in a 100-ms interval at the beginning of the vowels of the one-syllable naturally spoken consonant–vowel–consonant words /bAk/ and /dAk/ were manipulated. The resulting continuum had 10 levels with F2 onsets gradually situated at higher frequencies, making the fall of the transition steeper at every step; for more details, see [20]. Categorical perception studies showed that the 50% classification point was situated between levels 3 and 4, and that discrimination between levels (e.g. between levels 3 and 6) is problematic in dyslexic individuals. We therefore took these levels and contrasted them in an oddball design with level 3 as the standard stimulus (F2 onset frequency of about 1280 Hz) and level 6 as the deviant stimulus (F2 onset frequency of about 1460 Hz). Deviants were randomly presented with 10% probability in a block of 500 trials. At least three standards were presented between successive deviants. Stimulus onset asynchrony was 800 ms and stimuli (620 ms duration, 75 dB sound pressure level) were (binaurally) presented by speakers at 70 cm from the infant's head. The infants were lying in a child's safety seat while stimuli were presented and brain activity was recorded. The total duration was about 11 min. All infants were tested during quiet sleep, which is an advantage when assessing preattentive processing because it diminishes the influence of confounding cognitive factors, and minimizes movement artefacts.

Electroencephalogram recording, processing and analysis

A 32-channel electroencephalogram was recorded with 500 Hz per channel and filter settings 0.01–100 Hz (Synamps model 5083, Neuroscan Inc., El Paso, Texas, USA). Infant caps (Easy Cap, FMS, Munich, Germany) with sintered Ag/AgCl electrodes included all 10–20 system locations (Oz, O1/2, Pz, P3/4, P7/8, CPz, CP3/4, TP7/8, Cz, C3/4, T7/8, FCz, FC3/4, FT7/8, Fz, F3/4, F7/8 and Fp1/2). Additional electrodes were used for recording the vertical electrooculogram (above and below the left eye) and the horizontal electrooculogram (at the outer canthus of each eye). The ground electrode was placed at AFz and reference electrodes were attached to the mastoids. Impedance was kept below 20 kΩ. The electroencephalogram was digitally band-pass filtered (1–15 Hz, 24 dB/octave), and artefacts exceeding $\pm 125\,\mu V$ in any channel were rejected from analysis (Brain Vision Analyzer, Brain Products, GmbH, Munich, Germany). Individual grand average ERPs were determined for standards and deviants, and for the mismatch response (deviants–standards). The ERPs were transformed to the average reference for all subsequent calculations. Differences between the infant's brain responses to standards and deviants were assessed by topographical analysis of variance (TANOVA; [22]) on raw maps. Sources of the mismatch responses were estimated by low-resolution electromagnetic tomography analysis (LORETA) [23], which computes the smoothest possible current source density solution (in grey matter) without a priori assumptions about the number of generators.

Results

The bootstrapping TANOVA procedure revealed significant differences ($P < 0.05$) between standards and deviants for the control infants only, and this difference never reached significance levels for the infants at risk (Fig. 1). For the control infants, significant mismatch detection was found between 449 and 563 ms (after stimulus onset), which encompasses a positive mismatch response, and between

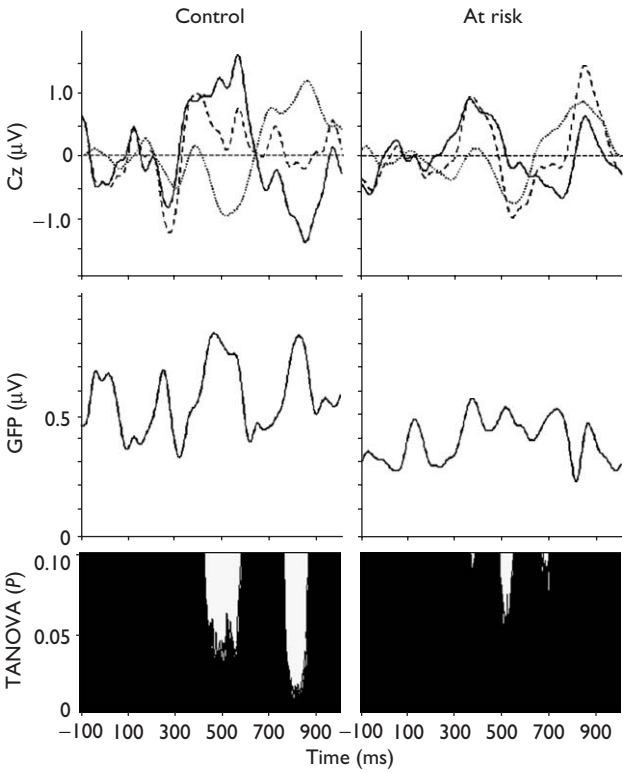

Fig. 1 Lower panels (left for controls, right for at risks) show the *P*-values of the mismatch response computed with topographical analysis of variance (TANOVA). Values below 0.05 indicate significant (amplitude) differences between standard and deviant maps. The TANOVA panel for the controls shows two significant mismatch periods, but *P*-values for the at-risk group never reach significance. Middle panels show global field power (GFP) amplitude for the mismatch response. Note that there are two distinct GFP peaks in the time window in which TANOVA reaches significance for the control infants (left). Upper panels show event related potentials at Cz for standards (dashed lines) and deviants (dotted lines). Deviance responses (solid lines) are present only for the controls.

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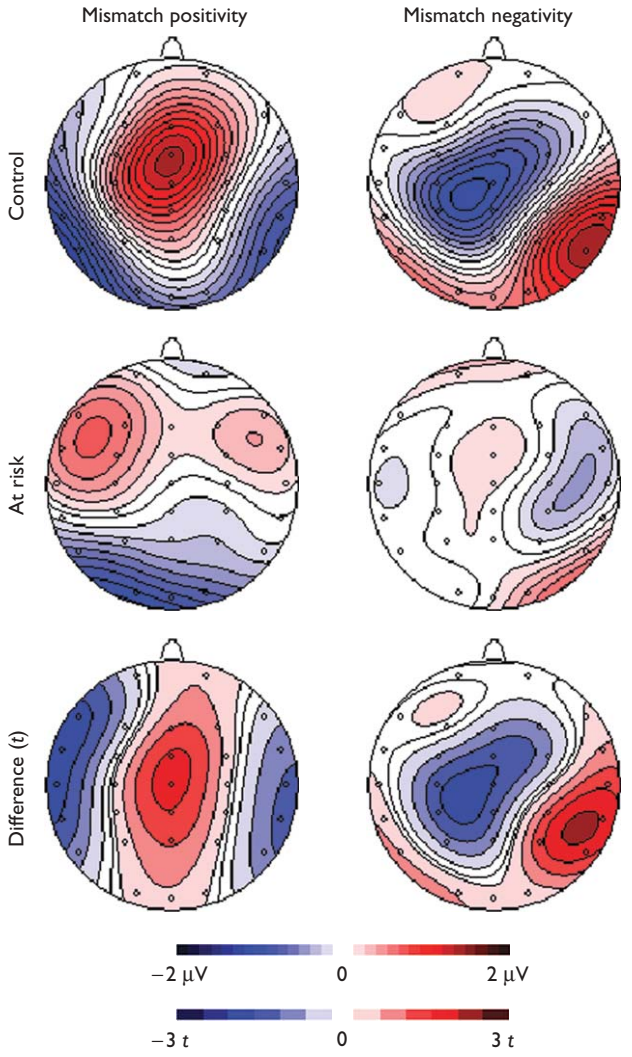

Fig. 2 Topographical maps for controls (upper panels), showing frontocentral mismatch positivity and (left) frontocentral mismatch negativity. Middle panels show the difference maps for infants at risk. Lower panels show *t*-maps of the difference in mismatch responses between the groups at frontocentral areas for mismatch positivity, and (left) frontocentral and right temporal–parietal areas for mismatch negativity.

763 and 853 ms, indicating a negative mismatch response. To further explore the deviance response in the control infants, individual mismatch responses were averaged and global field power (GFP; a measure for electric field strength) was computed. GFP segmentation yielded major microstates (epochs with relatively stable topographical maps) between 484 and 598 ms and between 650 and 868 ms (Fig. 1), consistent with the TANOVA windows. Next, mean GFP in the TANOVA periods and mean values for separate electrodes were tested in an analysis of variance (ANOVA). For mismatch positivity, differences between standards and deviants were found for GFP [$F(1,17)=43.75$, $P<0.0001$] and for P8 [$F(1,17)=4.74$, $P<0.05$], TP8 [$F(1,17)=5.77$, $P<0.05$], T8 [$F(1,17)=7.03$, $P<0.05$], P7 [$F(1,17)=5.58$, $P<0.05$], Cz [$F(1,17)=6.63$, $P<0.05$], TP7 [$F(1,17)=7.34$, $P<0.05$] and FCz [$F(1,17)=10.08$, $P<0.01$]. For mismatch negativity differences between standards and deviants were found for GFP [$F(1,17)=26.03$, $P<0.0001$] and O2 [$F(1,17)=6.99$, $P<0.05$], P4 [$F(1,17)=11.35$, $P<0.01$], P8 [$F(1,17)=13.94$, $P<0.01$], TP8 [$F(1,17)=9.24$, $P<0.01$], CP3 [$F(1,17)=4.98$, $P<0.05$] and C3 [$F(1,17)=9.73$, $P<.01$]. Additional *t*-tests directly compared the mismatch responses between groups (although mismatch responses were not significant in the at-risk group), and showed significant frontocentral differences for both the positive and the negative mismatch responses (Fig. 2). A further ANOVA with group as a between-subjects factor confirmed this observation by showing a group by mismatch interaction at separate electrodes: CPz [$F(1,48)=6.12$, $P<0.05$], Cz [$F(1,48)=5.19$, $P<0.05$] and FCz [$F(1,48)=5.45$, $P<0.05$] for mismatch positivity, and similarly at P4 [$F(1,48)=4.7$, $P<0.05$], TP8 [$F(1,48)=6.32$, $P<0.05$], C3 [$F(1,48)=6.85$, $P<0.05$] and a trend at P8 [$F(1,48)=3.95$, $P=0.053$] for mismatch negativity. Post-hoc analysis showed that differences between standards and deviants emerged in the control group only, which is consistent with the TANOVA results. Finally, LORETA was used to clarify the sources of the mismatch responses in the control infants, showing clear cortical activity at the superior temporal auditory cortices in the control infants, but such sources were absent in the infants at risk (Fig. 3).

Discussion

This ERP mapping study set out to explore whether reported impairments in the perceptual differentiation between the stop consonants /b/ and /d/, or syllables /ba/ and /da/, in dyslexic individuals is already present in infants at familial risk for the disorder. In order to clarify that question, we tested quietly sleeping infants at risk and controls in an oddball paradigm employing two manipulated consonant–vowel–consonant speech stimuli at either side of the phonemic boundary and recorded the brain's automatic deviance response. Surprisingly, it turned out that our carefully selected group of infants at risk for dyslexia was unable to preattentively detect the deviance between the two levels that were taken from the continuum, as is evident from the TANOVA (Fig. 1), so there was no mismatch detection. Such ERP differences between infants at risk for dyslexia and controls have not been reported before for phonemic category deviance. Differences in mismatch detection between at-risk infants and controls, however, have been reported before for differences in phonemic duration rather than category, for example by Friedrich *et al.* [24], with infants at risk for specific language impairment, and in infants at risk for dyslexia, reported by Leppänen *et al.* [12]. Here, we show a striking lack of phonemic deviance detection in the at-risk infants, which is an important finding because at 2 months of age it may already point to problematic consonant differentiation at a later age. The auditory stimuli employed here only differed in the amount of frequency change with time in the second formant of the utterances, as these became progressively more rapid. The at-risk group's insensitivity to these changes thus supports Tallal's basic auditory temporal processing deficit hypothesis [5] and may indicate an early neurobiological marker of the disorder. The control infant's brain responses did show sensitivity to the subtle differences between the two manipulated speech stimuli. In fact, two mismatch responses could be observed, mismatch positivity at about 450 ms and mismatch negativity at about 760 ms (Fig. 2). Moreover, as is evident from Fig. 3, LORETA produced clear temporal cortical sources for both these

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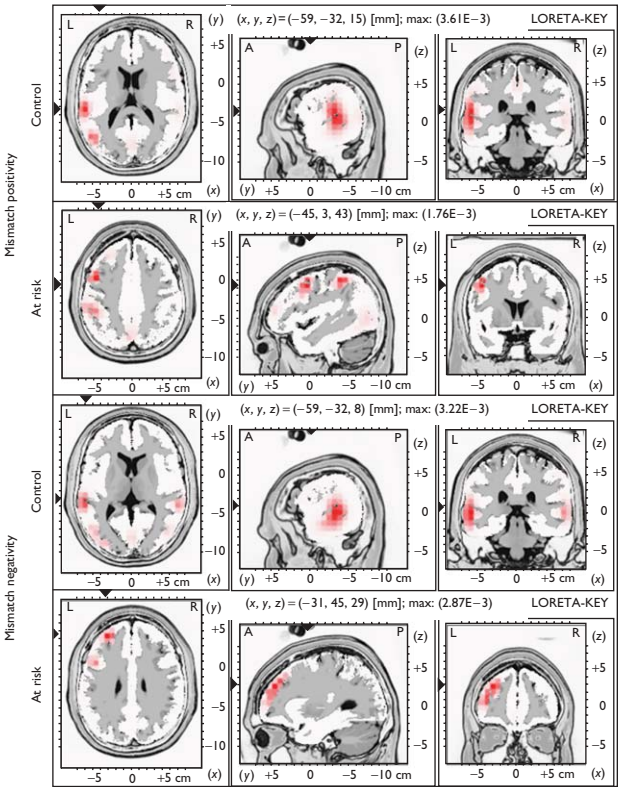

Fig. 3 Low-resolution electromagnetic tomography analysis (LORETA) sources of averaged potential maps for mismatch positivity (upper panels) and mismatch negativity (lower panels) for controls and infants at risk. Temporal sources were found in the controls only and were more pronounced at the left hemisphere for mismatch positivity and were bilateral for mismatch negativity. Talairach coordinates (*x*, *y*, *z*) and the maximum of LORETA values (also with black triangles) are indicated. L, left; R, right; A, anterior; P, posterior.

mismatch responses, somewhat more lateralized to the left for mismatch positivity and a bilateral distribution for mismatch negativity. The nonappearance of such auditory cortical sources in the at-risk group further underlines this group's mismatch impairment. Given the nature of the manipulated speech stimuli [20], we should correct the latencies of the mismatch responses for the silent murmer period, which is about 190 ms. So, mismatch positivity occurs at about 260 ms and mismatch negativity occurs at 570 ms. Interestingly, both latencies (given the young age of our infants) and distribution of the present mismatch responses are consistent with recent findings reported by Maurer *et al.* [25]. They found mismatch positivity and mismatch negativity at comparable latencies with kindergartners (including a group at familial risk for dyslexia) with difficult phonemic (naturally spoken *ba* and *da*) contrasts, and showed similar cortical sources. Positive mismatch responses have been reported before in infants [16,18], but with the present results found in the control infants we extend these observations by showing that the pattern found by Maurer *et al.* [25] – mismatch positivity followed by mismatch negativity – is already present in infants.

Conclusion

Already at the age of 2 months, infants at familial risk for dyslexia can be differentiated from control infants on the basis of their automatic brain responses to phonemic deviance. This observation is important because sensitivity to differences between phonemes is a prerequisite for learning to read. Follow-up studies will clarify whether the impaired deviance responses in the infants at risk reflect their elevated risk for the disorder.

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