Auditory Sensory Impairment in Children With Oral Clefts as Indexed by Auditory Event-Related Potentials

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Children with nonsyndromic oral clefts and with the CATCH 22 syndrome (acronym for cardiac defects, abnormal faces, thymus hypoplasia, clefts, and hypocalcemia) display a range of language and learning disabilities, the neurofunctional bases of which are not yet understood. This review summarizes recent event-related brain potential (ERP) studies on central auditory processing in infants and children with different cleft types and presents an effort to integrate these ERP and earlier behavioral findings into a workable hypothesis on the mechanisms of cognitive impairment in the oral cleft population. The encoding of the acoustic sound features and the functioning of auditory sensory memory (ASM) were studied by recording cortical auditory ERPs. Tapped were two ASM functions: tone pitch discrimination and the duration of sensory memory for tone pitch. In infants with cleft palate, tone pitch discrimination was impaired at birth and at 6 months of age. In infants with cleft lip and palate, no ASM impairment was detected at either age. In school-aged children with clefts and CATCH 22 syndrome, the discrimination of tone pitch was intact under optimal stimulation conditions. However, in these children, shortened duration of ASM was observed, with the magnitude of its shortening covarying with cleft type and being most pronounced in children with CATCH 22 syndrome. The different types of ASM dysfunction found in children with different cleft types could not be accounted for by the peripheral hearing deficits. The relation between ASM dysfunction and known behavioral cognitive disability profiles in children with different cleft types suggests that ASM is implicated in language disabilities of children with oral clefts. Furthermore, it appears that the ASM impairment and oral clefting are linked in a comorbid fashion.

Key Words: Auditory impairment, CATCH 22 syndrome, oral clefts, event-related potentials (ERPs), mismatch negativity (MMN)

The goal of the event-related brain potential (ERP) studies reviewed here was to determine the nature and indices (if any) of the CNS involvement in cleft-associated cognitive impairment. Since the predominant cognitive disability in children with oral clefts is language impairment, auditory sensory memory (ASM), which is known to be implicitly involved in language acquisition and everyday usage, was targeted as a possible dysfunctional module. Further, because sound processing at the cortical level can be affected by the peripheral hearing status, the present work related current ERP findings to the available information on hearing in children with oral clefts. Finally, since the utilization of auditory information in verbal communication represents the end product of the sound-processing continuum, the implications of the observed ASM dysfunction for the learning and language disabilities in children with oral clefts will...
be discussed. In the following, the genetic background, hearing, and language performance pertinent to different cleft types are concisely described.

**GENETIC BACKGROUND**

Oral clefts constitute approximately two thirds of the major craniofacial malformations with an incidence of 0.5 to 2 per 1,000 live births.\(^2\)\(^-\)\(^4\) Clefts of the lip and/or palate may occur in isolation (nonsyndromic), or they may be associated with other inborn malformations (syndromic). Current evidence suggests that nonsyndromic oral clefts are genetically based, with defects occurring in the major gene locus(es) encoding proteins that mediate the fusion of the mouth roof tissues.\(^2\),\(^5\),\(^6\) Epidemiologic and genetic studies suggest that cleft lip (CL) and cleft lip and palate (CLP) and cleft lip/alveolus (CL/A) might be caused by the same defects in the genome, whereas the genetic bases of isolated cleft palate (CP) are believed to differ from those of the CLP and CL/A.\(^1\)

Syndromic clefts, comprising up to 20% of all cleft cases,\(^4\),\(^7\) can be caused by chromosomal abnormalities (i.e., large genome defects where multiple genes or even a whole chromosome is absent or in excess). However, a majority of syndromes involving clefts are genetic in origin just as the nonsyndromic clefts are.\(^8\) Syndromic clefts constitute but one symptom from a cluster of structural and functional abnormalities that are often seriously debilitating. The CATCH 22 syndrome (acronym for cardiac defects, abnormal faces, thymus hypoplasia, clefts, and hypocalcaemia\(^8\),\(^9\)\(^-\)\(^10\)) has the greatest incidence of oral clefting.\(^11\),\(^12\) This syndrome is caused by a microdeletion in chromosome 22 and is considered to account for the variants that were earlier known as velocardiofacial (VCF), DiGeorge, and cardiotruncal syndromes.\(^13\),\(^14\) The most common cleft type in CATCH 22 syndrome is CP, with its incidence varying from 56% to 100%.

**CLEFT TYPE AND LANGUAGE AND LEARNING DISABILITIES**

The general IQ of children with nonsyndromic oral clefts is usually within the normal range, albeit at its lower limit.\(^16\) In addition to defective speech, up to 46% of these children have been shown to display specific language disability,\(^17\) apparently contributing to their poor learning performance.\(^18\) It has not been uncommon to attribute these language deficits to peripheral hearing loss or articulation defects.\(^19\),\(^20\) This account is challenged by studies showing no or only a poor relationship between hearing and language disability. Instead, a suggestion was made that cognitive impairment in the oral cleft population is genetically predetermined and linked to cleft type.\(^21\),\(^22\) However, studies on cognitive performance in children with different cleft types have yielded rather diverse results. One study\(^23\) found the general and verbal IQs of 5- to 11-year-old children with clefts to be within the published norms. Several other studies found impaired verbal performance in infants and children with oral clefts\(^24\),\(^25\) but no differences between those with different cleft types were obtained.\(^22\),\(^26\),\(^27\)

Nonetheless, the most common finding in the oral cleft population was that children with CP perform more poorly than those with CLP.\(^21\) Children with CP often have impaired language comprehension, association, and reading skills, whereas children with CLP show expressive language deficits such as poor phonemic repertoire and poor intelligibility.\(^28\),\(^29\) Importantly, the comprehension deficits characteristic of CP children are more detrimental to cognitive development than are the expressive difficulties.

Studies on infants with oral clefts are still rare. An interesting study by Scherer and D’Antonio\(^30\) followed the development of play gesture, imitation, and language in four CLP and two CP toddlers from 20 to 30 months of age. This method allowed overcoming of methodological difficulties when evaluating language development in a speech-impaired population. It was found that CLP children progressed normally on play and language growth but showed delay in expressive language use, whereas the toddlers with CP showed gesture as well as expressive and receptive language deficits.

In older children, reading disability was found in 50% of 6- to 7-year-old, 30% of 8- to 9-year-old, and 20% of 10- to 13-year-old children (N = 172).\(^31\) In the oldest group, the incidence of reading disability in CLP children was comparable to that in the general population (9%), whereas in those with CP, it was considerably higher (33%). Further, Richman\(^32\) found that at the age of 4 to 5 years, delays in language, vocabulary, and memory were equally frequent across different cleft types but that at the age of 7 to 8 years, only boys with CP remained linguistically impaired. Similarly, boys with CP comprised a majority of 46% of children with oral clefts who showed learning disability at the age of 6 to 18 years.\(^17\)

To the best of our knowledge, only one study has found children with CLP performing more poorly than those with CP.\(^33\) The authors reported
differences in the Mental Scale Index of the Bayley Scales of Infant Development \(^3\) between infants and toddlers with CL, CP, CLP, and Pierre-Robin sequence \((N = 180)\). In contrast to the previously cited findings in school-aged children, young patients with CLP scored significantly lower than their controls in this study, with those with CL being at the upper limit of the normal range and those with CP being at the instrument mean. Further, it was found that during infancy, the best predictors of developmental delay were visuomotor coordination scales, whereas language expression or understanding became predictive only after the age of 15 months. Such a sequence appears logical, since language deficits may become more evident with increasing complexity of and demands on language skills with age.

Therefore, in the nonsyndromic oral cleft population, there appears to be a relation between age, the severity of cognitive impairment, and its pattern. During the first year of life, infants with clefts show average developmental scores, with their performance declining during early childhood. During the school years, language performance gradually improves and the cleft-type specific disability patterns emerge.

In contrast to children with nonsyndromic oral clefts, virtually all those with CATCH 22 syndrome suffer from more severe cognitive disability.\(^1\)\(^2\)\(^3\)\(^5\) The IQ in these children is at the lower limit of the normal range or slightly below it; in the majority of cases, they require additional tutorial assistance.\(^3\)\(^6\) The mental handicap in CATCH 22 syndrome is generalized and involves linguistic, associative reasoning, concept formation, communication, mathematics, and motor coordination skills.\(^3\)\(^6\)\(^7\) A recent follow-up study of four VCF children aged 6 to 30 months revealed substantial delays in receptive (especially expressive) language compared with healthy, CP, and CLP children.\(^8\)\(^9\) In another study,\(^9\) development, language, and speech delays in 13- to 36-month-old CATCH 22 syndrome children were associated with the chromosomal deletion and not with the presence of clefts, cardiac defects, or surgery. Therefore, in CATCH 22 syndrome, the relationship between oral clefting and cognitive disability has been difficult to determine.

**Middle Ear Disease and Verbal Intelligence**

One of the factors considered to feasibly link oral clefting and language disabilities is conductive hearing loss. It is caused by middle ear disease (MED), a noninfectious middle ear effusion caused by dysfunction of the Eustachian tube. Newborns with oral clefts are included in a high-risk register for hearing loss,\(^1\)\(^0\) since MED develops in a majority of them.\(^1\)\(^7\)\(^1\)\(^8\)\(^9\) Infants with clefts are thus exposed to varying levels of auditory sensory deprivation during the period of language acquisition, which might contribute to their learning and language problems. Consistent with this, Reyes et al.\(^4\) found a correlation between chronic MED and hearing loss in children with VCF. Further, two recent studies\(^2\)\(^6\)\(^2\)\(^7\) in cleft children aged 12 to 30 months found a relationship between language proficiency and peripheral hearing loss but not between language proficiency and cleft type. However, whereas some studies showed a correlation between the peripheral hearing loss and verbal abilities,\(^2\)\(^0\)\(^2\)\(^6\) others failed to do so.\(^1\)\(^9\)\(^2\)\(^1\)\(^3\)\(^4\)\(^4\) Jocelyn et al.\(^4\) found that even though hearing status at the age of 12 months correlated with some language measures at the age of 24 months in CLP infants, it did not account for all language delays detected, especially at the older age. Even less clear is the relationship between hearing loss and the cognitive impairment profiles associated with different cleft types. So far, no differences have been found in the MED incidence or extent of the hearing loss in children with CP, CLP,\(^4\)\(^6\) or CATCH 22 syndrome,\(^4\) whereas the characteristics of cognitive impairment appear to differ among these groups.

Most importantly, by school age, the middle ear problems in cleft children are largely resolved and their hearing thresholds normalize,\(^4\)\(^7\)\(^4\)\(^8\) whereas cognitive disabilities at this age differ as a function of cleft type. These data indicate that certain cognitive deficits in the oral cleft population might be independent of impaired articulation, peripheral hearing loss, or the presence of cleft or somatic complications, as in CATCH 22 syndrome cases.

**Theoretical Rationale for Research Approach**

Studies reviewed in this article used cortical ERPs to study CNS functioning in a population with oral clefts. Analyzed were the obligatory ERP components reflecting automatic (preconscious) sound detection and sound feature encoding\(^4\)\(^9\)\(^5\) and the mismatch negativity (MMN) potential\(^5\) allowing testing of ASM, which provides sensory bases for conscious auditory perception. Such an approach permitted investigation of well-defined stages of central auditory processing in individuals with oral clefts. In view of the fact that the incidence of MED is the same regardless of cleft type, differences in the ASM functioning between children with different cleft types would provide evidence of a primary CNS
deficit playing a role in their language and learning disabilities.

ASM is the earliest memory buffer within which information about sound properties (e.g., its spectral content, intensity, source location) is stored for a short period of time.52 The sensory module of short-term memory operates automatically or preconsciously, that is, independently from conscious sound perception or evaluation, thereby protecting the higher order auditory processing from an overload by irrelevant sensory input. Importantly, temporary lingering of all sensory information in ASM provides both a "database" and time for the selection of relevant information by attentional mechanisms and for its read-out to the conscious processing stages.53 ASM is substantially implicated in language acquisition and its everyday use. During language acquisition, the formation of short-term neural representations of speech sounds is an indispensable step toward their consolidation into the long-term memory codes of one’s native language.54,55 Young language learners do not use the conscious memorization and rehearsal strategies available to adults.56 In children, auditory input (e.g., a spoken sentence) is available for phonological coding, comprehension, or memorizing for only as long as it is maintained in ASM. Further, the accuracy of sensory speech sound coding appears to affect the quality of the corresponding neural phoneme codes.57

Due to its preconscious nature, it is difficult, if possible at all, to investigate ASM using behavioral methods. Any test requiring voluntary sound evaluation is “contaminated” by top-down processes such as motivation, ability to concentrate, familiarity with the test sounds, and ability (skills) to respond. In contrast, elicitation of the MMN requires no active attending or responding,58,59 thereby providing an exceptional measure for direct investigation of ASM.

The MMN is generated bilaterally in the auditory cortices,60 with the frontal lobe systems modulating the temporal lobe activity.61 The MMN reflects preconscious detection of change in the auditory environment, which is accomplished via a comparison process between the incoming auditory input and the short-lived neural representation of the invariant aspects of recent auditory history.59,62 The MMN is typically obtained by presenting sequences of identical or "standard" sounds to a subject, which are randomly replaced by a different or "deviant" sound (oddball paradigm) in 10% to 20% of trials. If the sound change exceeds the perceptual discrimination threshold, that is, if the subject can behaviorally detect the change, the MMN is elicited.53-65 In addition to permitting an objective evaluation of cortical auditory discrimination, the MMN enables one to investigate a decay function of the ASM traces, since the MMN can no longer be elicited after the ASM trace of the repetitive sound has decayed.58 ASM durability is thus studied by prolonging the interstimulus intervals. Due to its close correlation with conscious perception, the MMN measure is useful when studying uncooperative or language-impaired patients, infants, and prelingual children. As indexed by the MMN, sensory sound discrimination was impaired in children with developmental dysphasia,66-68 learning disability,69 and dyslexia,70 that is, in the conditions most often encountered in the oral cleft population.

Therefore, the studies reviewed here investigated ASM as possibly being implicated in cleft-associated cognitive disabilities. The purpose was to determine whether ASM functioning is impaired in children with oral clefts and, if so, whether ASM dysfunction correlated with cleft type. The rationale behind the second question was that if language learning disabilities in cleft children develop as the sequelae of sensory deprivation, which does not vary across cleft types, there should be no consistent differences in ASM functioning between children with different cleft types. In contrast, if ASM dysfunction correlated with cleft type, this would provide evidence of primary CNS involvement in cleft-associated cognitive disabilities.

This series of studies71-75 was conducted by the Cleft Center, Department of Plastic Surgery, Helsinki University Central Hospital and Cognitive Brain Research Unit of the University of Helsinki. As the evidence accumulated, a need to systematize the experience and to formulate a synthesized workable hypothesis on the nature of and the mechanisms behind cleft-associated cognitive impairment became apparent. The work at hand aimed at accomplishing this goal by reviewing the results obtained by these studies and by integrating them in the context of available information on hearing and language in children with oral clefts.

**Materials and Methods**

**Infant Subjects**

Altogether, 32 full-term normal birth weight (22 male) infants with oral clefts were investigated at the mean age of 10 days after birth.73,75 Among them, 4 (3 male) infants had CL, 17 (9 male) infants had varying degrees of CP, and 11 (10 male) infants had unilateral or bilateral (n = 3) CLP. Twelve healthy full-term (6 male) newborns investigated at
the mean age of 5 days comprised a control group. Fifteen of those cleft (11 male) infants who were tested as newborns were also investigated at the mean age of 6 months and 8 days. One of them had CL, 6 had CLP (all male), and 8 had CP (4 male). The control group at this age consisted of 8 healthy (3 male) infants, with a mean age of 7 months and 2 days. None of the infants had any accompanying disease or identifiable syndrome.

Children

Seventy-eight (49 male) children with oral clefts (mean age: 8 years and 2 months) born in Finland during 1989 and treated at the Cleft Center of the Helsinki University Central Hospital were selected for the present project.34 Thirty-two age-matched healthy (14 male) children (mean age: 8 years and 3 months) comprised the control group. The selection criteria for the cleft children were: 1) the cleft was nonsyndromic, 2) no present conductive hearing loss, and 3) no mental retardation. None of the control children had hearing, speech/language, or academic achievement problems as reported by their parents. Children with clefts were subdivided on the basis of the clinical examination of the anterior-posterior position of the cleft (Fig. 1). The subgroups were CL or CL/A, complete unilateral cleft of lip and palate (UCLP), and CP. The CP cases were further subdivided according to the anterior-posterior extent of the lesion into clefts extending to the incisive foramen (CP1), those extending to the area between the incisive foramen and soft palate (CP2), those of the soft palate only (CP3), and submucous clefts of the soft palate (SMCP).

Eleven (4 male) children with CATCH 22 syndrome (mean age: 8 years) were tested with the same study protocol as that used in school-aged children with clefts. The CATCH 22 syndrome diagnosis was made at the Helsinki University Cleft Center and was verified by fluorescent in situ hybridization (FISH) chromosome analysis. All CATCH 22 syndrome patients were identified as language impaired according to the history of their speech and language development; clinical status; and results of available Wechsler Intelligence Scale for Children–Revised (WISC-R),76 Neuropsychological Assessment of Children (NEPSY),77 and Illinois Test of Psycholinguistic Abilities (ITPA) test batteries. Six of these children were also impaired on phonological memory tests. Patients, healthy infants, and children were recruited with their parents’ informed consent. Ethical permission for the study was obtained from the Helsinki University Central Hospital.

Stimuli and Procedure

The stimuli were 1,000- and 1,100-Hz sinusoidal tones (100 milliseconds in duration and 75 dB sound pressure level in intensity). The 1,000-Hz tone served as a standard and was presented with 90% probability. The remaining 10% of the sounds were randomly occurring 1,100-Hz deviants (i.e., the standard and deviant tones differed in pitch). The stimuli were presented in blocks of 500 tones. In infant studies,73,75 the interstimulus interval (ISI, offset-to-onset interval) between the successive tones was randomly occurring 1,100-Hz deviants (i.e., the standard and deviant tones differed in pitch). The stimuli were presented in blocks of 500 tones. In infant studies,73,75 the interstimulus interval (ISI, offset-to-onset interval) between the successive tones was randomly occurring 1,100-Hz deviants (i.e., the standard and deviant tones differed in pitch). The stimuli were presented in blocks of 500 tones. In infant studies,73,75 the interstimulus interval (ISI, offset-to-onset interval) between the successive tones was 700 milliseconds (Fig 2, top). In school-aged children, a decay rate of the ASM traces for the same 1,000-Hz tones was tested in addition to the pitch discrimination.71,72,74 To this end, the standard and deviant tones were presented in separate blocks with three different ISIs of 350, 700, and 1,400 milliseconds (see Fig 2, bottom).

In a portion of the infants, an additional “deviant alone” condition (see Fig. 2, top) was used.73,75 In
this condition, the 1,100-Hz tones were presented with no intervening 1,000-Hz standard tones but with the timing identical to that in the oddball sequences. The deviant alone condition was carried out to evaluate the obligatory components of the ERPs that index transient sound feature coding but not the discrimination between different stimuli.59

Experiments were conducted in an acoustically and electromagnetically shielded chamber (Ari Nummela, Ltd, Finland). The tones were produced by NeuroStim equipment and played via two loudspeakers located on both sides of the subject at the head level. Newborn infants were lying on an experimental couch or in a parent’s lap between the loudspeakers. The 6-month-old infants were sitting either in a safety seat or in a parent’s lap. School-aged children were sitting in a comfortable armchair watching voiceless cartoons of their choice. All subjects were visually monitored throughout the experiment. The EEG was recorded (30-Hz DC, 250-Hz sampling rate) using NeuroScan software. Stimulus onset-locked EEG intervals of 850 milliseconds were digitally epoched and sorted according to the stimulus type (standard or deviant) and condition and averaged off-line.

Data Analysis

The MMN appears as a negative displacement in the deviant-sound ERP relative to the standard-sound ERP at approximately 150 to 300 milliseconds from the onset of sound change. For the purposes of MMN visualization and measurements, deviant minus standard ERP difference waves were constructed. In this series of studies, the amplitudes of the obligatory ERPs and the MMN were measured as a mean voltage of the brief periods (80 milliseconds in infants and 50 milliseconds in children) centered at the latencies of the corresponding peaks of each subject. Two-tailed t tests were used to determine the statistical presence of the obligatory peaks and the MMN, that is, whether their amplitudes differed from the prestimulus baseline, which was equated to 0 μV. ANOVAs for repeated measures were performed to look for the between-group and between-condition differences in the obligatory ERP and MMN latencies and amplitudes.

RESULTS

Infant Mismatch Negativity

In a pilot study on nine newborns with isolated CP and eight healthy newborns,73 evidence of impaired preconsciously sound discrimination in CP neonates was found. Only 3 of them showed an MMN kind of response. As a group, the CP infants’ responses to the deviant tones were positive relative to those elicited by the standard tones (Fig. 3). In contrast, healthy newborns’ responses to the deviant tones were negative relative to the standard tone responses, with this negative difference being taken as the MMN. The MMN amplitudes differed statistically between healthy newborns and those with CP ($F(1,14) = 7.85, P < 0.02$).

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When a larger number (n = 32) of cleft newborns were divided into CP and CLP groups, significant differences between their MMNs were found (Fig 4, top). The CP newborns showed no MMN kind of response, whereas CLP neonates displayed an MMN comparable to that of their healthy peers. The MMN in the CP subgroup was smaller than that of both the healthy peers and CLP infants (post hoc test: $P < 0.02$ and $P < 0.003$, respectively). When 15 of the cleft infants were retested at the age of 6 months, the CLP infants' MMN did not statistically differ from that in control infants, whereas those with CP showed no second component of the MMN at the latency range of 300 to 500 milliseconds (late difference negativity [LDN]; see Fig. 4, bottom). The difference in the LDN amplitudes between healthy and CP infants was significant at $F(1,14) = 13.85$, $P < 0.0023$.

Infant Responses to Standard and Deviant Alone Stimuli

ERPs to the identical sound presented at either a fast or slow pace (in the current studies, the standard and the deviant alone, respectively) reflect sound detection and transient encoding of its acoustical features but not feature discrimination. In both CP and CLP newborns, the standard 1,000-Hz tones elicited a rather low-amplitude ERP dominated by a positive deflection (Fig. 5, top left). This positivity was significantly greater in healthy infants than in both CP and CLP infants ($F(2,34) = 7.27$, $P < 0.002$). Importantly, no differences were found in the standard ERP amplitudes between the CP and CLP infants. At the age of 6 months, there was a tendency ($P < 0.08$) for the healthy and CLP infant responses to be larger in amplitude than those of the infants with CP (see Fig. 5, top right). However, the CLP infants also showed an abnormal ERP waveform, lacking the negative peaks.

At newborn age, the deviant alone ERPs showed a strong tendency ($P < 0.07$) to be smaller in amplitude in infants with either cleft type than in their healthy peers (see Fig. 5, bottom left). Important, as with the standard ERPs, no differences in the deviant alone responses between the CP and CLP newborns could be found. At the age of 6 months, the deviant alone ERPs tended to be smaller in infants with oral clefts than in their healthy peers (see Fig. 5, bottom right). Unfortunately, the small number of subjects at this age did not allow comparison of the cleft type subgroups.

Mismatched Negativity in 7- to 9-Year-Old Children

ASM dysfunction was subtler in cleft children at the age of 7 to 9 years and differed in a finely graded manner as a function of cleft type. With a short 350-
millisecond ISI, no differences in the MMN amplitudes were found between the CP, CLP, CATCH 22 syndrome, and healthy children (Fig. 6).\textsuperscript{72,74} With slower stimulation (700-millisecond ISI), the MMN in CATCH 22 syndrome children was significantly smaller than that in their healthy peers ($F(1,20) = 19.95, P < 0.001$), although not statistically different from the cleft children’s MMN. It was only the slowest stimulus rate (1,400-millisecond ISI) that revealed a significant MMN amplitude attenuation not only in the CATCH 22 syndrome children ($F(1,20) = 12.93, P < 0.002$) but in CP children ($F(1,20) = 6.49, P < 0.02$).

In order to test the relation between ASM decay and cleft type in the nonsyndromic cleft population, the data were arranged by six subgroups of children with nonsyndromic clefts (see Fig. 1) who were compared with each other and with their healthy peers.\textsuperscript{74} Again, no differences between the MMNs of healthy children and those with any type of cleft were found with two shorter ISIs (Fig. 7, top), whereas with the slowest stimulation (1,400-millisecond ISI), the MMN amplitude of all cleft children (as one group) was significantly diminished compared with that of the controls (post hoc test, $P < 0.00002$; see Fig. 7, top). Among the subgroups of children with CP, a systematic MMN diminution was observed; that is, the more posteriorly delimited the cleft was, the smaller was the MMN amplitude (post hoc test, $P < 0.04$; see Fig. 7, bottom). In children with CL/A and CLP, the MMN findings unexpectedly diverged. The CL/A children’s MMN did not differ from that in healthy peers, whereas in children with complete unilateral CLP, the MMN was smaller in amplitude than that in any other cleft subgroup (post hoc test, $P < 0.0002$).

Responses to Standard Sounds in 7- to 9-Year-Old Children

No differences in the standard tone ERPs were found between the healthy children and those with any cleft type.

DISCUSSION

This article reviews recent ERP studies on central auditory functioning in infants and children with different cleft types. An impairment of preconscious discrimination of tone pitch was found in infants.
with CP but not in those with CLP. In school-aged children, the dysfunction of central auditory processing manifested as shortened duration of short-lived memory traces for tone pitch, with the magnitude of this shortening depending on cleft type. In the following, we will discuss the implications of these findings on the current understanding of the nature of cognitive impairment in children with oral clefts.

Relation Between Cleft Type, Peripheral Hearing, and Mismatch Negativity Findings

At birth, the ERPs to the standard and rare (deviant alone) stimuli were smaller in amplitude in both CP and CLP newborns than in their healthy peers. At 6 months of age, the standard tone ERPs tended to be smaller in amplitude in CP infants than in CLP or healthy infants; however, the waveform structure of the standard ERP was abnormal in both CP and CLP infants.

A question arises regarding the extent to which these pathological findings might have been caused by the compromised peripheral hearing. Literature on MED in children with clefts indicates that these children do have depressed hearing likely impeding their auditory and language skills, especially at younger ages. No study, however, reported differences in peripheral hearing measures among infants or children with different cleft types. In the studies reviewed here, the cleft newborns were investigated at the mean age of 10 days (range: 4–19 days). By this time, a middle ear effusate had likely accumulated in most of them, regardless of cleft type. This correlates well with the finding of abnormal obligatory responses at birth occurring independently of cleft type and suggests that diminished obligatory responses in infants reflect reduced input from the auditory periphery to the central mechanisms of audition.

However, the possibility that dysfunction of the central auditory systems contributes to the obligatory ERP findings cannot be ruled out, especially at the age of 6 months. At this age, the obligatory responses were abnormal in both CP and CLP infants; however, they were abnormal in different ways. Infants with CP showed a tendency for diminished amplitude of the main (positive) peak in the standard stimulus ERPs, whereas the ERPs of infants with CLP were comparable in amplitude to those in the controls. Nonetheless, the waveform structure of the CLP infants’ responses was immature; just as at the newborn age, it lacked the negative peaks.

In contrast to the obligatory responses being abnormal in both CP and CLP infants, the MMN was abnormal in the CP group only. As indexed by the MMN, in infants with CP, the impairment of preconscious tone pitch discrimination was found at birth and also at 6 months of age. In contrast, in infants with CLP, the MMN was comparable to that in their healthy peers at both ages. These differences in sound discrimination abilities between infants with CP and CLP appear to be unrelated to the peripheral hearing status or to the auditory processing underlying the generation of the obligatory responses. There is evidence indicating that auditory obligatory ERPs and the MMN are generated by different neural systems. Therefore, ASM functioning might be affected independently of the processes underlying generation of the obligatory ERPs, which appears to be the case in the CP infants. Having said this, we would like to emphasize that peripheral hearing loss most likely has a general impact on the development of auditory-based functions in children with clefts. As found in the present studies, it is only the differences between cleft types that are suggested to be unaccounted for by the peripheral hearing deficits.

School-aged children with oral clefts showed no abnormalities in the obligatory ERP components elicited by the standard stimuli, which is consistent with normalized peripheral hearing in the oral cleft population at this age. Furthermore, school-aged children with any type of cleft or CATCH 22 syndrome showed no MMN amplitude differences with fast (350-millisecond ISI) stimulus presentation. This indicates that these children can preattentively discriminate sounds under optimal conditions, that is, when the ASM trace is easy to build up (frequent reinforcement of the trace) and the discrimination between sounds is easy (perceptually, a 1,100-Hz sound is easily detected among 1,000-Hz sounds by children and adults).

However, the MMN diminution with the long 1,400-millisecond ISI signified a serious pathological finding in some of these children. It implied that the short-term maintenance of auditory information is impaired in the proportion of children with oral clefts. In school-aged children, the pattern of the MMN diminution was related to cleft type in a systematic fine-graded fashion (Fig 7, bottom), which could not be linked to either the peripheral hearing deficits or the abnormalities in the obligatory responses. Children with CL/A displayed MMNs comparable to those of their healthy peers, whereas children with CP, as a group, showed a moderately, although significantly, diminished response. Among the CP children, the more posteriorly delimited the cleft was, the smaller was the MMN amplitude ob-
served. Children with unilateral CLP showed the fastest decay of sensory memory.

CP and CLP probably have different genetic origins; therefore, it is possible that different pathophysiological mechanisms with different ontogenetic timings are implicated in these two cases. On the basis of the MMN findings in children and infants, it seems feasible to assume that auditory sensory discrimination and the persistence of ASM are preferentially impaired in CP and CLP patients, respectively. Furthermore, the even faster ASM decay found in CATCH 22 syndrome children corresponds to more severe and generalized cognitive disabilities. Besides the specific language impairment, CATCH 22 syndrome children exhibit generalized mental retardation. Therefore, in this syndrome, the central auditory dysfunction is likely to be only one of the components of a more general cognitive disorder.

The finding of the shorter ASM persistence in CLP than in CP children was entirely unexpected, since most of the behavioral data indicated that CLP children perform better at school or on language tests than children with CP. A possible explanation of this discrepancy is the fact that in the majority of behavioral studies, children with CLP were pooled with those with CL/A on the basis of their common genetic origins. However, children with CL/A typically do not suffer from learning or language disabilities (nor do they show an abnormal MMN); in addition, they constitute a considerable proportion (up to 38%) of the CL/A + CLP population. Therefore, pooling CL/A and CLP children in behavioral studies has likely masked the cognitive deficits of children with CLP. Another possibility is that children with CLP have a type of CNS dysfunction that has not been tapped by the earlier behavioral studies. Indeed, the number of studies finding impaired language or auditory skills in CLP children is increasing.

Relation Between Cleft Type, Mismatch Negativity Findings, and Language Disability Profiles

In behavioral research, all but one study found delayed or impaired cognitive functioning in children with oral clefts, with the language deficits prevailing consistently. In light of the fact that ASM plays an important role in language acquisition and everyday functioning, it is likely that the dysfunction of ASM found in the ERP studies in infants and children with oral clefts is implicated in their language and learning disabilities.

Most of the studies that compared language performance in children with different cleft types found that children with CP produce lower test scores than those with CLP. The ERP studies reviewed here found that in the CP subgroup, the impairment of pitch discrimination persisted throughout the infancy, that is, during the time period of crucial importance for language acquisition. Such a deficit may result in “noisy” phonological representations of the speech sounds that are formed during the first year of life. Poorer quality of the neural sound representations in the short-term memory can also cause their faster decay, as found in the CP group at the age of 7 to 9 years. Therefore, early deficit in auditory sensory discrimination might be one of the important pathogenetic factors manifested in the form of the persistent perceptual problems of children with CP.

In contrast, in children with CLP, the shortened ASM span appears to coexist with their good cognitive skills, including language. As already mentioned, one of the reasons why language disability in children with CLP might have been overlooked in the behavioral studies is the fact that most of these studies have pooled children with CLP together with those with CL/A. Another explanation of this discrepancy might be provided by the nature of their ASM dysfunction. We found that the duration of the ASM traces (but not auditory sensory discrimination as such) is impaired in the CLP group. There is both behavioral and ERP evidence that sensory memory span lengthens during development. Therefore, it is feasible that the deficit in ASM duration amplifies with time, along with the lengthening of the ASM span itself. An immediate implication of this phenomenon would be a later onset of this type of dysfunction, which would take place during the later stages of language development. Most interestingly, the aforementioned study by Kapp-Simon and Krueckeberg found that the developmental delay in CLP infants is aggravated from 6 to 18 months, which is in line with the present hypothesis of the amplification of detrimental ASM dysfunction effects with age. This similarity of the developmental trajectories of the behavioral disability and ASM shortening in children with CLP permits one to link the two, even though the nature of this connection is yet to be established. Finally, the distinct consequences of the different types of ASM impairment (discrimination versus memory decay) might be caused by the “online” sound feature discrimination deficit being more detrimental to language development than the shortened duration of sound representation in memory.

During the first year of life, infants with clefts show average developmental scores. Their per-
formance significantly declines during the preschool years, however, regardless of cleft type. This might be attributed to the amplifying effects of relatively mild language disabilities when the verbal communication requirements increase. Only during the school years do the cleft-type specific behavioral disability patterns appear to emerge. This is probably related to the improving hearing and thus to the elimination of the deficit common to all cleft types as well as to the increasing demands on mental performance.

The Hypothesis of Comorbidity Between Oral Clefting and Central Nervous System Dysfunction

The ERP evidence reviewed here converges on suggesting that there are differences in auditory sensory functioning between children with different cleft types that are not contingent on the peripheral hearing loss or on the auditory processing underlying the generation of the obligatory ERP components.

What, then, underlies these different impairment profiles observed in both the present study and in many behavioral studies? During the early phases of embryogenesis, the cell pools that give rise to the facial and cerebral structures are located close to each other (facial tissues are derived from the neural crest cells) and share a number of biological mediators that govern organ and tissue formation. For instance, the neural cell adhesion molecule (NCAM) plays a crucial role in the fusion of the palatal shelves, axonal growth, synaptogenesis, and regulation of neuromediator levels in the developing brain. Other biologically active substances, for example, transforming growth factor-α (TGF-α), steroid hormones, and retinoic acid, are also implicated in both cerebral and cleft-tissue morphogenesis in various ways. Therefore, cell-signaling molecules similar to NCAM might possibly be at the root of both cleft and cerebral phenomena. However, much more integrated research linking the embryogenesis of different cleft types with cognitive disability profiles is needed before this hypothesis could be tested. It would be important to investigate ASM functioning by using cleft classification based on the emerging definition of a number of embryogenetic mechanisms leading to the formation of different cleft types.

CONCLUSIONS

The ERP studies reviewed here suggest that some of the children with oral clefts display deficits in ASM that are not accountable for by the peripheral hearing loss, because the type (discrimination or memory) and the timing (infancy or childhood) of this central auditory disability differ between children with different cleft types, whereas peripheral hearing does not. Therefore, it appears that both oral clefting and ASM dysfunction can be caused by common genetic substrates affecting both early embryonic development and neuromediation during postnatal life. Consequently, it is suggested that there is a primary CNS impairment in the oral cleft population and that oral clefting and language disability are related in a comorbid fashion.

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and its magnetic counterpart (MMNm) elicited by sound


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