The Development and Neurophysiological Assessment of Newborn Auditory Cognition: A Review of Findings and Their Application

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ABSTRACT

This review article introduces the basic principles of infants' neurophysiology, while summarizing the core knowledge of the anatomical structure of the auditory pathway, and presents previous findings on newborns' neural speech processing and suggests their possible applications for clinical practice. In order to tap into the functioning of the auditory pathway in newborns, recent approaches have employed electrophysiological techniques that measure electrical activity of the brain. The neural processing of an incoming auditory stimulus is objectively reflected by means of auditory event-related potentials. The newborn's nervous system processes the incoming sound, and the associated electrical activity of the brain is measured and extracted as components characterized by amplitude, latency, and polarity. Based on the parameters of event-related potentials, it is possible to assess the maturity of a child's brain, or to identify a pathology that needs to be treated or mitigated. For instance, in children with a cochlear implant, auditory event-related potentials are employed to evaluate an outcome of the implantation procedure and to monitor the development of hearing. Event-related potentials turn out to be an irreplaceable part of neurodevelopmental care for high-risk children e.g., preterm babies, children with learning disabilities, autism and many other risk factors.

KEYWORDS

newborns; auditory pathway; cortical auditory evoked potentials; maturation of the central nervous system; learning disabilities

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INTRODUCTION

The neonatal period is defined as the interval from birth to the 28th day of an infant's life. Despite being marked by its beginning and end points, the neonatal period should – in many respects – be understood as a direct continuation of intrauterine development. According to knowledge of auditory perception, it is well-established that the fetus can hear and process surrounding stimuli and adequate prenatal auditory stimulation is necessary for normal development of hearing (1, 2).

After birth, hearing becomes one of the fundamental senses that stimulate the early development of a child's cognitive functions, thus contributing to the acquisition of speech, language, and abstract thinking. Intact peripheral and central part of the auditory apparatus is necessary for a child's psychomotor development. As hearing impairment may interfere with cognitive and psychomotor development, it is crucial to detect this deficit as soon as possible. Subsequent intervention, e.g. with a cochlear implant (CI), may reduce impact on all aspects of later life quality (3–7). For this reason, objective screening methods focused on auditory perception are typically performed. The most common is the assessment of transient evoked otoacoustic emissions (TEOAE). This approach can assess the functionality of cochlea (the peripheral part of the auditory apparatus) but cannot measure whether the information has also been correctly processed by the

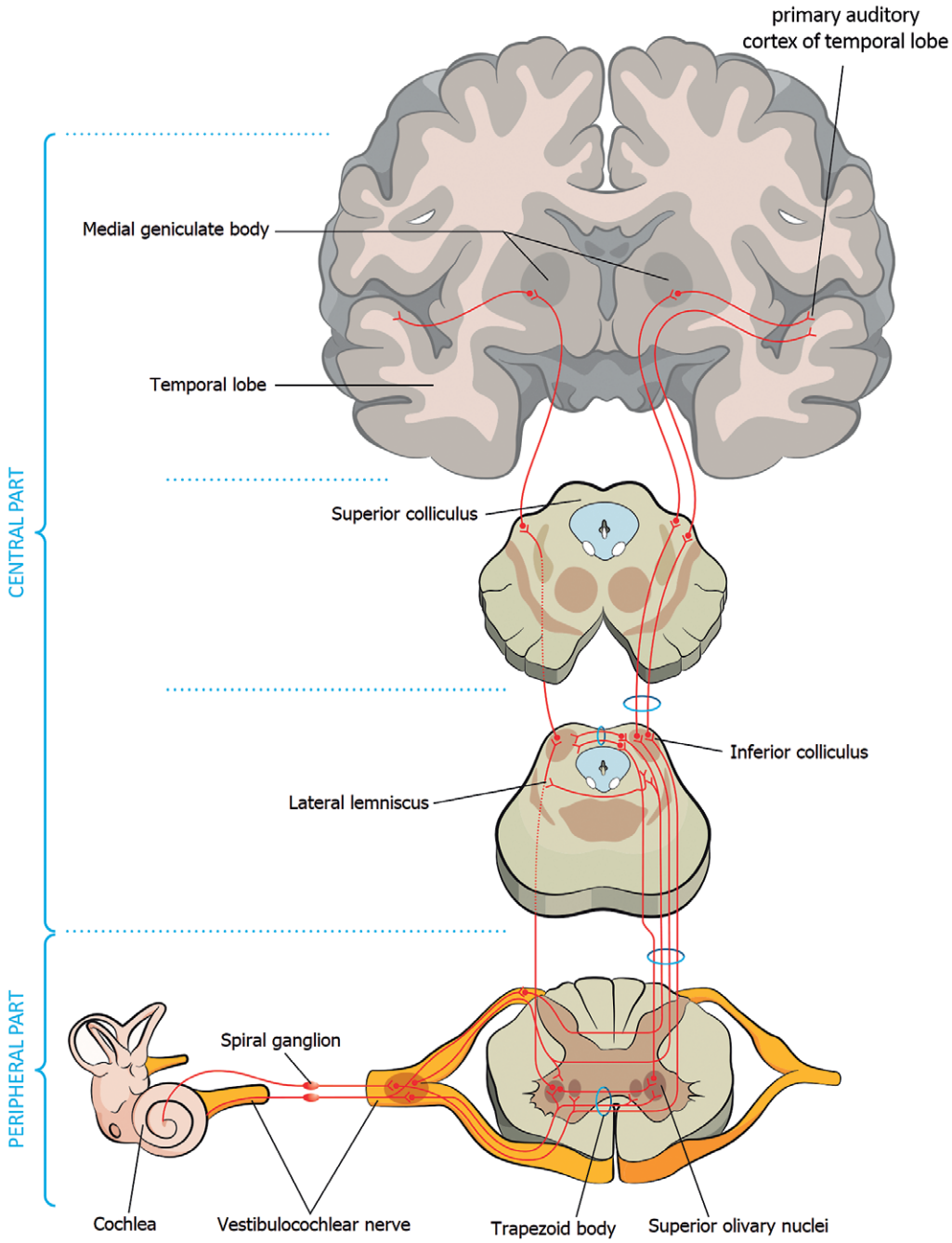

Fig. 1 Anatomical structure of the auditory pathway can be divided into a peripheral part, including the cochlea as a sensory organ, and a central part that conducts electrical potentials through the brain stem and midbrain to the primary cortical region, where it is subsequently evaluated and processed (scheme adopted and freely modified according to (1)).

central nervous system (CNS). Improper engagement and functioning of the higher auditory areas can lead to disorders such as the auditory processing deficit, dyslexia, or learning disability (3, 8). Detection of the brainstem, early, and later evoked potentials, also called event-related potentials (ERPs), allow us to examine the subsequent stages of auditory stimulus processing. These techniques objectively test the functional integrity of the auditory system by measuring the brain's response to auditory stimuli (9).

ANATOMY OF AUDITORY PATHWAY

The auditory pathway is distinguished into the peripheral and the central part, also called structural and neurosensorial, respectively (Figure 1). These two parts differ not only in their function, but also in the timeline of their development. The peripheral part consists of the outer, middle, and inner ear. It participates in capturing and converting an incoming auditory stimulus (mechanical sound waves) into electrical potential, which is transferred to the central auditory system (1). The division of the peripheral system into the outer, middle, and inner ear mostly follows the development of primary germ layers or their derivatives (Figure 2A–D). The base of the inner ear forms at the beginning of the fourth gestational week and its development completes in the 20th gestational week (1, 10, 11).

It is through the vestibulocochlear nerve that the auditory receptor potential reaches the brainstem, afterwards switching to the mesencephalon, thalamus, and finally the cerebral cortex. The primary auditory cortex is in the temporal lobe, in the tonotopically arranged area 41 (Figure 1). The axons end in the associative cortical regions areas 42 and 22. This part of the auditory system does not develop fully until the 20th gestational week (12, 13).

The cochlea of the inner ear and the auditory cortical networks in the temporal lobe are, developmentally, the most sensitive clinical components of the auditory pathway. They may be affected during intrauterine

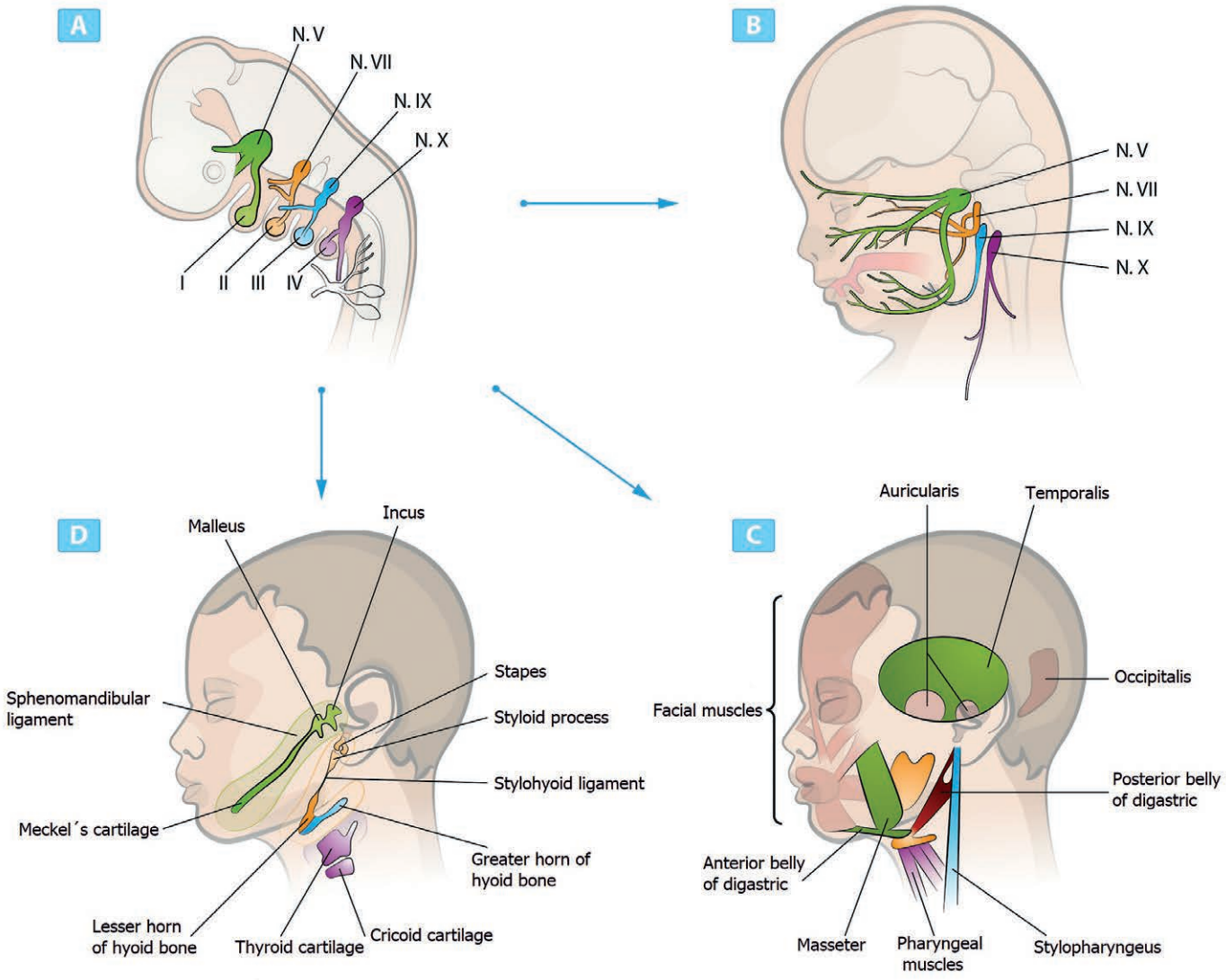

Fig. 2A–D Diagram of the gill arches and their development (marked with Roman numerals I-IV, color distribution respects the origin of tissues from individual arches also in the following figures B–D). Figures A and B also show the origin of cranial nerves important for innervation in the facial region (labeled N.V-N.X). The gill arches I and II give rise to the transmission system of the middle ear, the peripheral part of the auditory pathway. Gill arch I also develops into the tensor tympani muscle, which participates in the transmission of sound by changing the drum voltage (scheme adopted and freely modified according to (11)).

development, e.g. by prenatal infection, but also in the neonatal period due to antibiotic treatment, or exposure to noise in a neonatal intensive care unit (14). This vulnerability stems largely from the gradual maturation of the sensitive neurosensory part (the hair cells of the inner ear), axons and neurons, that takes place between the 25th gestational week and the fifth month of life (1).

The auditory pathway can transmit the surrounding sound stimuli to the developing fetal brain already between the 25th and the 29th gestational week. During gestation, the uterus is a natural barrier protecting the fetus from intensive impacts that could harm its development, limiting the intensity as well as the spectral content of the incoming sound (1, 3, 15). However, even in the rather attenuated and somewhat distorted sound, a physiologically developing fetus can recognize various frequently encountered sounds, most notably the rhythm and melody of its mother's speech (16). Prenatal auditory stimulation aids the development of the tonotopic organization of the cochlear hair cells and the auditory cortex (14). After birth, when the attenuating barrier disappears, the incoming auditory stimuli contribute to further cortical development. From the perspective of hearing, the neonatal period is an uninterrupted continuation of intrauterine development (1, 2). This is evidenced by a study that compared the development of hearing with vision. While vision develops only after birth, auditory stimulation with varied naturalistic stimuli (e.g. maternal voice, music, or common environmental sounds) during the last 10–12 weeks of the fetal period *in utero* or in prematurely born infants seems to be essential for proper hearing development (1).

CORTICAL EVOKED POTENTIALS

Neuronal activity induced by auditory stimulation can be detected as evoked potentials, at many different levels of the auditory pathway. The measurement of evoked potentials is a non-invasive, dynamic, and objective method based on the principle of electroencephalography (EEG) sensing the electrical activity of the brain. Cortical Auditory Evoked Potentials (CAEPs) are often measured to assess auditory perception. They belong to a broader group of ERPs, sometimes called cognitive ERPs (9). ERPs extraction is done by averaging epochs of the EEG that are aligned to the occurrence of repeatedly presented acoustic stimuli (12, 17).

To assess the trajectory of auditory processing one typically evaluates the components, i.e. the peaks and their latencies, within the averaged ERPs. The advantage of the ERP method is its fine temporal resolution, which allows to accurately measure the peak time of a response, i.e., the latency, in milliseconds (9). The strongest CAEPs can be recorded in the back of lateral sulcus, the so-called Sylvian fissure, which separates the frontal and temporal lobes. Due to the non-invasive character of EEG recording the exact localization of CAEPs is not possible (12, 17).

With some simplification, CAEPs can be divided into exogenous (sometimes inaccurately called *obligatory*) and endogenous (inaccurately called *cognitive*) components. Exogenous components reflect the physical properties of the sound, such as the intensity, frequency, and duration, whereas endogenous components are modulated by neuronal activity in higher cortical centres and are not determined solely by the sound's physical properties (17).

Exogenous components include the P50, N100, P200, and N200. In newborns, unlike in older children, P100 and N100 waves are not well detectable. Newborns' ERPs typically have a relatively broad peak at 200–300 ms latency, called P200, which is followed by a broad negative N200 wave at 300–600 ms latency. The latencies and breadth of the P200 and N200 waves decrease markedly in the course of the first months after birth (9, 12).

Endogenous components are used to evaluate higher-level, e.g. linguistic, processing of auditory stimuli by the newborn brain. These components include the *mismatch response* (MMR) (18), P300, and N400. MMR, one of the most frequently evaluated components, is defined as a difference in the potential induced by a rarely occurring, i.e. *deviant,* stimulus, and the potential induced by a frequently repeated, i.e. *standard,* stimulus (Figure 3). The MMR is roughly interpretable as an index of prediction error originating from a comparison of a novel unexpected deviant stimulus against a built-up memory trace for the previously presented frequent standard stimuli (12). The MMR component is elicited automatically and does not require conscious attention to the stimuli, and can be also measured during (active) sleep. If a deviant sound is perceived as different from previously presented standard sounds, it elicits the MMR, typically at a latency of 100–250 ms relative to the onset of the deviation. The larger the perceived difference between the deviant and the standard stimulus, the larger the MMR amplitude and/or the shorter its latency. In adults, the MMR is typically bilateral in both temporal and frontal cortical areas (12) and has a negative polarity (hence in adults it is referred to as *mismatch negativity*, MMN, see Figure 3). In infants, however, MMR often has a positive polarity (3), indicating imperfect maturation and/or marginal audibility of the acoustic difference between the deviant and the standard stimulus (4).

Besides the age-related differential polarity, the MMR latency is in newborns greater than in adults and decreases gradually mainly during the first two years of life. Ontogenetically, the MMR is a very early potential detectable from the 30th postconceptional week (14, 17). Newborns' MMR, similarly to adults' MMN, reflects rather fine phonetic discrimination abilities, such as the ability to distinguish sounds coming from different sources, or the ability to detect both a change in speaker voice and in speech sound quality (9). This observation in healthy newborns indicates that the neonatal brain has a fully developed discriminatory capacity for sound stimuli (17), although its CNS structures are not yet fully mature (19–21). Newborns' MMR also indexes the ability to differentiate variations in auditory stimuli that are important for speech and language development (17). In child auditory perception, developmental speech disorders or learning difficulties are often associated with an attenuated or delayed MMR response (3). MMR is therefore well suited to assess the earliest stages of cognitive development, particularly the speech and language capacity of the developing individual.

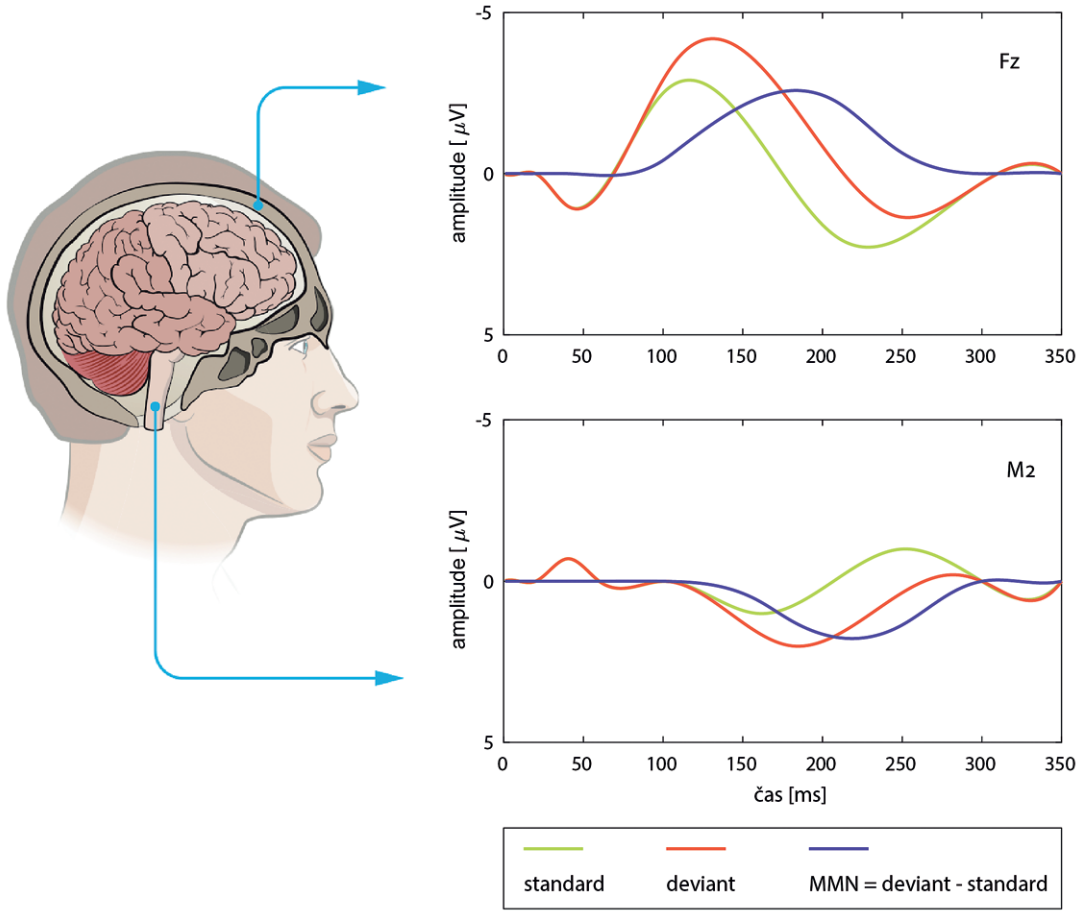

Fig. 3 Schematic representation of cortical auditory evoked potentials (CAEP) sensed by an electrode placed above the frontal area (Fz) and the processus mastoideus (M2). The frequent, standard stimulus is represented by a green curve, the rare, deviant stimulus by an orange curve. The subsequent amplitude difference of both stimuli is highlighted by a blue curve as the so-called difference wave, which peaks as mismatch negativity (MMN) at latency of about 200 ms. The amplitude of the MMN tends to be positive when measured with an electrode above the mastoid processus, in other locations it typically, in adults, has negative values (scheme adopted and freely adjusted according to (17)).

STUDIES WITH NEWBORNS

Several studies have assessed and evaluated auditory cognitive potentials in neonates. Most of studies test healthy newborns and apply inclusion criteria such as the absence of neurological disorders, medication, pre- or peripartal complications, excessive physical activity during the assessment, and need a passed neonatal hearing screening – brainstem auditory evoked potentials, steady state response auditors or TEOAE (4, 19). In previous studies, healthy newborns meeting the above criteria are typically compared to e.g. preterm newborns, infants with suspicion of hearing impairment, deficient neural speech processing, or high familial risk for a developmental language or speech disorder.

Melo et al. (2016) compared the cognitive evoked potentials of 31 preterm and 66 term infants. The infants were tested in sleep, after feeding, using biaural auditory stimulation. The syllable /ba/ served as the frequent standard stimulus, and /ra/ served as the rare deviant stimulus. The P100 and N100 waves were less likely to be present in preterm as compared to full term infants (they were missing in 13% and 4.5% of cases, respectively). No significant differences in the incidence of N200 or P200 were found between the two groups. The absence of the P100 wave in CAEP in premature infants can be a possible indicator of cognitive delays or immature cortical structures in this population. Besides evaluating the absence/presence of P100 (and N100), the latency of ERPs components can, be used too as an indicator of immaturity inversely proportional to gestational age (4).

The results of that study are in line with the results of other studies comparing the maturation of the infant brain. Exogenous components have longer latency in newborns than in older children, and the latency rapidly decreases in the first and second year of life. This may be caused by the development of synapses during the first years of life, reflected in an increase of low-frequency EEG activity, which is also the frequency range relevant for the ERPs. Continuing myelination at pre-school age leads to more adult-like ERPs.

In general, ERP latency thus mostly reflects the maturation of the CNS itself. ERP amplitude, on the contrary, seems to correlate with the number of neural structures involved in the response (number of synapses). Early developmental changes in the amplitude of the auditory ERP

thus seem to depend mainly on gestational age, and less so on the amount of (extrauterine) auditory exposure (2, 4, 20, 21).

A recent study by Oliveira et al. (2019) assessed CAEPs in 39 full-term newborns (19). The measurements were monoaural with a randomly selected ear stimulated by pure tones of various frequencies. At an initial sound intensity of 80 dB SPL, latency and amplitude did not show statistically significant differences for various stimulus frequencies. However, the latency of the P100 wave was inversely proportional to stimulus intensity. One of the conclusions of this study was that compared to the brain stem response, the cortical auditory ERPs are elicited only if stimulus intensity exceeds a particular threshold (2, 19). The fact that the brain stem response is elicited also at a lower stimulus intensity can be attributed to a faster maturation of the subcortical, compared to cortical centres. Some other studies found that the latencies of P100 and N100 are greater for pure tones than for speech stimuli (19, 22).

ERPs can be used not only to assess CNS maturation, but also to quantify the success of intervention in children with hearing disorders, especially with deafness. Silva et al. (2014) have shown that auditory cognitive potentials can verify the level of auditory stimulation needed for the maturation of the CNS in children with CI. For instance, there seems to be a relationship between the P100 wave, measured immediately after CI implantation, and the onset of vocalisation in children with different ages of CI implantation (6). After implantation, which positively affects the child's communicative development, one can objectively assess changes in the CNS, namely, a decrease of the P100 latency to tones and speech stimuli (4–7).

The CAEPs may assess the effect of CI implantation and normalization of auditory development but could also detect deafness in children. Mehta et al. (2017) described the role of the CAEPs for early diagnosis and later therapy in children with hearing loss in United Kingdom during 2011–2015. That study compared 2 sequential cohorts of children with a permanent childhood hearing impairment and with different time of CI implantation. The first cohort included 34 children examined prior the introduction of CAEPs, the second 44 children examined after the introduction of CAEPs. The only difference in the patient pathway was the use of CAEPs in diagnosis and therapy. Except the common examination, for the second infants group diagnosis included CAEPs to speech tokens /m/ (duration of 30 ms), /g/ (duration 20 ms), and /t/ (duration of 30 ms) presented at nominal intensity 55, 65 and 75 dB SPL. Early hearing aid fitting was recommended if the response for /g/ or /t/ at 55 dB SPL was missing. Additionally, a second CAEPs session 4 to 8 weeks later was performed for all children without a recommendation of early hearing aid at the first session. If the CAEPs (at second session) were absent at 75 dB SPL in infants optimally fitted with hearing aids, referral for CI assessment was recommended. The results showed that children with severe deafness were referred significantly earlier for CI assessment after the introduction of CAEPs than before: the median age of hearing aid fitting for children with all degrees of hearing impairment decreased from 9.2 months to 3.9 months after the introduction of CAEPs examination. This trend was observed also in children with mild or moderate hearing loss (median age decreased from 19 to 5 months) (7).

There are other areas in which CAEPs seem promising as an early diagnostic tool for developmental disorders. Thiede et al. (2019) performed a longitudinal study with 44 newborns at high familial risk of dyslexia and with a control group of 44 low-risk newborns. The newborns were stimulated by pseudowords with changes from a standard /tata/ stimulus in vowel duration /tata:/, vowel spectrum /tato/ and pitch /ta^{ta}/ at stimulus intensity 65 dB SPL. EEG recordings were analysed for MMR to each type of change. The results suggested atypical neural discrimination of speech sound differences in the high-risk newborns: their MMR were diminished or completely absent, had longer latency and different hemispheric lateralization and morphology compared to infants with no dyslexia in family history (3).

CONCLUSIONS AND CLINICAL APPLICATION

The auditory pathway is a necessary and irreplaceable connection of the developing fetus with the outside world. The peripheral and central auditory system development starts already in the prenatal period and at birth, hearing seems comparable in pre-term and term neonates (4). At the 40th gestational week, auditory cognitive potentials of premature and term-born infants do not seem to differ significantly, indicating that extrauterine stimulation does not alter the maturation of auditory processes in the pre- and postnatal period (17). Auditory ERPs display maturational changes throughout infants' development. Throughout infancy there is a clear developmental decrease in latency which is comparable across children born premature and children born full-term (same gestational age), despite the former group having had longer exposure to sounds *ex utero*, which aligns well with the gradual maturation of CNS structures across the intrauterine and extrauterine periods of development (19, 21).

The absence or reduced amplitude of ERP components can be used for diagnosis and evaluation of pathologies. As an example, MMR deficiency is often associated with learning disorders, cleft palate, autism or Asperger syndrome, depression or behavioural disorders. In children with very low birth weight and speech impairment, reduced MMR amplitude was found at four to six years of age (9). This reduction in MMR amplitude is to be associated with speech impairment rather than with the child's maturation at birth because, as noted above, the amplitude and latency of the measured cognitive potential components are comparable between term and very-low-birth-weight (premature) children (4, 17).

To conclude, electrophysiological methods are routinely employed to monitor neonatal hearing but here we show that they could have a greater application in the clinical practice as they can help assess the very development and maturation of the newborns' auditory pathway. Maturation of CNS depends primarily on the myelination of nerve fibers, which lead the signal to the corresponding

cortical centres which generate the cortical evoked potentials (19). Moreover, early and developmental evaluation of auditory ERPs is a promising approach that may find application in monitoring the dynamics of some developmental disorders and diseases such as dyslexia, autism (3, 8, 14). Based on recent findings which were reviewed in this article, we suggest that CAEPs should become an integral part of clinical practice to evaluate children's auditory development.

DEDICATION

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