The Role of Evoked Potentials (EPs) in the Assessment of the Human Central Auditory Nervous System (CANS)

P. Deltenre*, C. Colin**, B. Dachy*** and A.-L. Mansbach****

Université Libre de Bruxelles, *Clinique de Neurophysiologie & Institut d'Implant Cochléaire de l'ULB, CHU Brugmann, Bruxelles; **Unité de Recherche en Neurosciences Cognitives, Bruxelles; ***Clinique de Neurophysiologie, CHU Brugmann, Bruxelles; ****Service d'ORL pédiatrique, HUDERF & Institut d'Implant Cochléaire de l'ULB, Bruxelles

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Abstract. The Role of Evoked Potentials (EPs) in the Assessment of the Human Central Auditory Nervous System (CANS). This paper presents an overview of the use of EPs in the assessment of the CANS. Emphasis is laid on recent developments and research efforts centered on appraising how the auditory neural code is processed by the central pathways. It is shown how, in addition to their classical site-of-lesion testing role, EPs can, especially when combined with ecological (mostly speech-like) stimuli, yield highly valuable information on the neurophysiological processes leading to the perception of auditory objects as well as speech. Special space is devoted to the Mismatch Negativity that currently provides the only objective measure of the accuracy with which the CANS detects auditory and phonetic contrasts.

Introduction

From an anatomical point of view, the CANS begins at the point where the cochlear nerve crosses the meninges and exchanges its peripheral myelin for the central one. At this point, each single cochlear nerve axon, which is functionally equivalent to a primary sensory unit, already carries a portion of the peripheral neural code (See (1) for a review on the auditory neural code). Each piece of code has been created by the functional unit that a single nerve fiber constitutes with the Inner Hair Cell (IHC) it innervates. CANS lesions as peripheral as the intrameningeal portion of the cochlear nerve may therefore disrupt the primary neural code. Peripheral lesions along the extrameningeal portion can bring about the same result. Even intracochlear dysfunction of the entity formed by the presynaptic pole of IHCs, the synapse itself or the postsynaptic portion of cochlear nerve dendrites can alter the primary neural code. As soon as the first central relay is reached with the second order cochlear nucleus cells, parallel processing, a major feature of the CANS organization, is demonstrated as each primary sensory unit divides into several branches to deliver a copy of the neural code it carries to several types of cochlear nucleus neurons. Depending on the synaptic and membrane properties of each cell type, different stimulus-related information is extracted leading to parallel processing (2). Such parallel processing takes place further centrally in the CANS and is completed by a hierarchical type of processing. This means that information extracted at a lower level is recombined into synthesized features, which are recombined between themselves further centrally to build up what the eventual perception will be: a mental image of the sound source.

In real life, the job of the CANS can be pretty tough as noise or multiple sound sources can be simultaneously active, sending a rich mixture of sounds that the brain must sort out. Consider this simple example: a familiar voice is recognized by its timbre, which is itself defined by the spectral components it contains. In a noisy environment like a cocktail party, many other voices add a considerable amount of other spectral components and yet we still effortlessly recognize our friend's voice out of the lot. Auditory scene analysis (3) is the term that has been coined to describe this complex and ecologically vital function of the CANS. Most-if not all- CANS mechanisms rely on a normal peripheral cochlear analysis of the sound components present in the sound field so that most cochlear impairments will reduce the proficiency of the central processes. Some pathologic states like some forms of
presbycusis do comprise both peripheral and central deficiencies. Other ones like Obscure Auditory Dysfunction (OAD) or King-Kopetsky syndrome (4), Central Auditory Processing Disorder or CAPD (5) or even rare forms of Auditory Neuropathy (6) seem entirely due to an abnormal peripheral neural code or abnormal central processing since those patients exhibit normal peripheral hearing function.

Transmission, processing and elaboration of a gradually more and more complex neural code therefore constitute the basic function of the CANS. In addition to their traditional role in a site of lesion approach, EPs have recently proved to be a very interesting tool to assess parts of the neural code at various CANS levels (7). The organization of the present review is centred on the recent developments regarding neural code assessment, completed when indicated by the traditional site of lesion approach. Although traditionally the ascending CANS starts at the cochlear nucleus, we shall therefore adopt a somewhat original attitude and include the primary neural code level in the present review.

Primary neural code level

In the present state of the art of clinical neurophysiology of the auditory system, the abnormality of the primary code that is most easily detected is dysynchrony. The Auditory Brainstem Response (ABR) is exquisitely sensitive to reduced synchrony in the initial portion of the auditory pathways. This sensitivity made their success in revealing otherwise difficult to demonstrate lesions of the cerebello-pontine angle or lower brainstem before the era of modern imaging techniques. Despite the remarkable advances made by imaging techniques, the ABR remains a quick and cheap way to confirm a suspected cerebello-pontine angle or brainstem lesion. Currently, it is the concept of Auditory Neuropathy that occupies the forefront of audiologists' and speech therapists' concerns since its incidence reach a surprising 8-12% of subjects with a permanent hearing loss (8) and its management remains a therapeutic challenge (See (9) for a review).

Figure 1 illustrates how a disorder of the central myelin in a severe case of Pelizaeus-Merzbacher disease (10) can completely obliterate all ABR components after wave I that, because the peripheral, extrameningeal myelin is not affected, remains normal.

Whereas the click-evoked ABR combined with oto-acoustic emissions and Cochlear Microphonic recordings (11) are apt to detect primary code global dysynchrony, other techniques may offer a more focused view on peripheral encoding processes. There is currently a growing trend to use more natural stimuli than clicks or pure tones. This is based on the idea that the CANS has evolved under ecological constraints implying the processing of complex real-life sounds including vocalization sounds. At least one recent study (12) shows that some learning-impaired children who retain normal click-evoked ABRs exhibit ABR latency delays when stimulated with speech syllables presumably signaling a lower-level deficit not recognized with standard stimuli. Furthermore, it has long been recognized that in addition to the well-known tonotopic code, the stimulus frequency is, at least for frequencies below 3-5 kHz, encoded in a temporal mode. Low-frequency stimuli trigger action potentials during the acoustic rarefaction phase only (a phenomenon called phase-locking (13)) so that the time intervals between the action potentials code for the period of the stimulus. Any cochlear nerve fiber, irrespective of its characteristic frequency, can
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\[ 0.64 \, \mu V. \quad \text{vs.} \quad 1.88 \times 10^{-3} \, \mu V^2 \]

Peripheral and central FFRs recorded in a normal subject after stimulation with a missing fundamental harmonic series. The stimulus amplitude is modulated by a trapezoidal envelope. It consists of the third and fourth harmonics of a (missing) fundamental at 366 Hz (f0). The missing fundamental (f0) and its power spectrum have been added below the horizontal (H) and vertical (V) FFRs and respective spectra in order to demonstrate that in both the eighth nerve and brainstem response, the frequency content of the evoked waveform corresponds to that of the missing fundamental.

Fig. 2

Phase-lock to low-frequency stimuli and contribute to the temporal coding of their frequency. This is a mechanism by which correct pitch perception of low-frequency tones can be achieved in what has been called “off-frequency listening”, even when the corresponding tonotopic cochlear region is dead. The Frequency Following Response or FFR (14, 15) is an easily recordable evoked potential that reflects phase-locking and temporal encoding within the auditory nerve and the brainstem pathways. It is best recorded using a stimulus made up of several (two are enough) harmonics with a missing fundamental. This yields a perceived pitch corresponding to the missing fundamental (the well-known “missing fundamental affair” or “periodicity pitch” ; see (16, 17) for reviews) and an FFR at the frequency of the fundamental. This is a very practical way of avoiding artifact contamination since there is no stimulus energy, either electromagnetic or acoustic at the missing fundamental frequency. GALBRAITH (18) showed that the first stages of the pitch encoding-extraction process can be tracked by recording the missing fundamental FFR along a horizontal (earlobe-to-earlobe) axis yielding the cochlear nerve response, whereas a vertical, vertex-to-earlobe derivation shows phase-locking of the brainstem nuclei neurons. Figure 2 illustrates such FFRs recorded in our laboratory in a normal subject stimulated with a missing fundamental complex tone comprising two harmonics.

FFR recordings can not only contribute to the study of temporal encoding in the cochlear nerve and its processing within the brainstem, but also demonstrate the encoding of some acoustic traits known to be critical for speech recognition. This is potentially very interesting since the ideal result of auditory prostheses including cochlear implants is to restore a peripheral neural code as close as possible to the normal one. Speech perception studies have shown that encoding the first two formants of most vowels is sufficient for their identification and that neural phase-locking is the most robust basis for encoding the spectra of vowels (19-23). Moreover, the same temporal code is found in a sub-population of cochlear nucleus neurons (24). It has recently been shown (25) that Human scalp-recorded FFRs evoked by synthetic steady-state vowels contained spectral energy peaks corresponding to the first and second formants of the stimulating speech sounds. When consonant-vowels utterances are considered, an important acoustic trait differentiating for example a /da/ from a /ga/ (See figure 5) is the second formant transition. Formant transitions are rapid (20-40 msec) frequency changes that follow consonant burst and precede the stable, steady-state portion of the vowel. Recent data show that the Human FFR can also reveal the temporal encoding of this important acoustic cue (26).

Binaural processing

Among the numerous central processing schemes that take place as soon as the cochlear nucleus is reached, the brainstem auditory nuclei play a major role in auditory scene analysis thanks to the binaural integration process that takes place within the superior olivary complex in the pons. Specialized neurons with bilateral cochlear connections compare the intensity and time of arrival of the same auditory events reaching the two ears and from these data, compute the spatial localization of the sound source (See (27) for a review). Sorting the numerous sound components mixed in the sound field by their spatial origin
is for the CANS a major means of grouping them by sound source, thus reconstituting the mental images of the different sound sources. The Binaural Masking Level Difference or BMLD (See (28, 29) for reviews) is the most widely used psychoacoustic test to explore binaural integration at brainstem level. The BMLD is considered to be specifically sensitive to brainstem lesions (30). There have been many studies (See (31, 32) for extensive references) devoted to the development of an electrophysiological equivalent of the BMLD test, or at least to the demonstration of an interaction between left and right stimuli recordable in the form of a Binaural Interaction Component (BIC). If the BIC-ABR was the most widely investigated effect, recent studies were concerned with the BIC-FFR (33).

Midbrain, thalamic and temporal lobe levels: the Middle Latency Response

The Middle Latency Response (MLR) consists of up to 6 components \((N_{a-s}, P_{a-s}, N_{a-s}, P_{a-s}, N_{a-s}, P_{a-s})\) with latencies ranging from 8 to 50 msec. Component \(P_{a-s}\) is often incorporated as \(P_{a-s}\) or \(P_{a}\) of the long-latency “Vertex” potential (See section a). The involved anatomic generators extend from the midbrain and auditory thalamus \((N_{a-s}, P_{a-s})\) to the primary \((N_{a-s}, P_{a-s})\) and secondary \((P_{a-s})\) auditory cortex (See Table 1 in (34)). There are suggestions (35, 36) that the human MLR is a composite response from primary and non primary auditory pathways. The thalamus is the most peripheral location at which behavioral hemispheric asymmetries have been reported in response to speech stimuli (37). MLRs have been successfully used to document unilateral hemispheric lesions (38) as well as bilateral lesions leading to cortical deafness (39, 40). Since MLRs receive contributions from auditory cortical regions that are closely related to speech recognition and language function, they have been used, with some success, in efforts trying to correlate them with high-order speech processing (41). Unfortunately, the MLR suffers from a very protracted maturational course responsible for a high level of variability within the paediatric population (See section on maturation). They are also very sensitive to sleep and drowsiness as well as to most sedative and anaesthetic drugs. These properties significantly reduce their usefulness for the assessment of clinical individual cases. The MLR has also been used in order to investigate binaural interactions (42).

Temporal, parietal and frontal lobes level: the Long Latency Response

With the Long Latency Response (LLR), we enter a latency region within which a distinction must be made between exogenous and endogenous evoked potentials components. Exogenous or “obligatory” components are potentials that are, given a normal subject, entirely defined within normal ranges of morphologies, amplitudes and latencies by the stimulus parameters. Endogenous or “non-obligatory” components are mainly determined by the type of processing that the subject’s brain applies to the stimulus-related incoming information. The stimulation paradigm that is most commonly used in order to evoke endogenous evoked potentials is illustrated in figure 3 and is called the oddball paradigm. It is made up of two stimulus categories: a frequent (or standard) one with a typical occurrence rate of 80-90% and a rare (or deviant) one. The rare stimuli appear randomly within the series of frequent ones. The potentials evoked by either category are computed separately so that any difference between the waveforms evoked by the rare and the frequent stimulus can be measured. The amplitude of most endogenous evoked potentials is inversely related to the probability of the rare stimulus (43).

a. The exogenous \(P_{1-s}, N_{1-s}, P_{3-s}\) complex

Space constraints do not allow a detailed description of the several bilateral generators located in the temporal and frontal lobes that are implied in the generation of the \(P_{1-s}-N_{1-s}-P_{3-s}\) to quote typical latencies. \(N_{1-s}\) which is made up of at least three components, (a temporal one, a tempo-parietal one and a frontal one) reflects the conscious detection of any discrete change in any subjective dimension of the auditory environment as well as (frontal component) attention switching to the stimulus. It is an onset response reflecting synchronous neural activation of the thalamo-cortical pathway in response to acoustic change. The interested reader will find updated reviews in (34, 44).

When recorded with a reference electrode on the tip of the nose, the \(N_{1-s}, P_{3-s}\) component exhibits a clear polarity reversal across the sylvian fissure (typically, between a vertex or parietal electrode and a mastoid one). This typical polarity distribution has been used to
The oddball stimulation paradigm. Within a train of frequently presented standard stimuli, deviant stimuli that are to be contrasted with the standards are presented with a low probability of occurrence. The EPs to standards and deviant are collected separately. White triangles indicate the Ni (down-pointing) and P3 (up-pointing) components. Black triangles indicate Pm. The type of endogenous waveform elicited by presentation of deviant stimuli is contingent on the subject's cognitive involvement: When he is actively counting the deviants, a late positive wave (P3W : see section d) is evoked. When the subject ignores the sequence content and is engaged in a distractive task, an extra negativity (the Mismatch Negativity : see section c) is evoked at about 100-200 msec. The endogenous nature of the potential evoked by deviance is compellingly demonstrated by the occurrence of an isolated P3W wave when the attended deviant consists in the absence of a stimulus in an otherwise regular sequence.
Mismatch Negativity elicited by a difference in duration (standard 100 msec, deviant 50 msec) between two sound bursts with a frequency of 1 kHz and an intensity of 60 dB SL. A grand average has been performed across two normal subjects. The MMN is isolated by subtracting the waveform evoked by the deviant delivered by itself (deviant alone: thin upper trace) from the waveform evoked by the deviant mixed within the standard sequence (deviant in seq: thick upper trace). The up-pointing arrow indicates the point in time that defines the MMN latency, here the termination of the shorter stimulus, which is the earliest point in time at which deviance can be noticed. The MMN has a peak latency of 144 msec.

Several studies indicated that the sensory memory traces probed by the MMN underlie the auditory (echoic) sensory memory (62). The MMN can therefore also be used to assess the echoic memory (63). The MMN is generated in the temporal auditory cortices with an additional contribution from the frontal cortex (64). The latency of the MMN is inversely related, and its amplitude positively related, to the magnitude of the difference between the standard and the deviant stimuli. With respect to clinical applications, it escapes several general unfavorable features of endogenous (cognitive) evoked potentials: the latter are significantly dependent on the subject's attentional state and are depressed by anaesthetic and sedative drugs, so that they do not hold much promise for the testing of uncooperative or communicatively incompetent patients. The MMN is a notable exception because it is already present in normal newborns (65), is automatically elicited without any need for active collaboration by the subject (66), and is correlated with behavioral discrimination (67). Another major advantage with respect to paediatric applications is that the MMN remains recordable during sleep (68, 69). These properties

deleterious effect of aging on the neural encoding of the VOT and the cumulative effect of aging and hearing loss when the latter was present. In yet a different field of application, another recent potentially interesting use stems from the demonstration that among children with Auditory Neuropathy, those who retain recordable LLRs seem to be the ones who will benefit from amplification (56).

b. N2

Research efforts using the oddball paradigm led to the discovery of the N2 (or N2a) component (57), which is also sensitive to the probability of the deviant stimulus (58). N2 presence requires attention to the deviant stimulus and the waveform does not invert its polarity at the mastoid. After the subsequent discovery of the Mismatch Negativity (MMN: see section c), which occurs within the same latency region, N2 has been subdivided into N2a (nowadays called the MMN) and N2b (now called N2). N2 has been found severely abnormal in patients with attention deficit disorders (59). It can be elicited following either a physical discrimination task or a semantic discrimination task, the former being a passive attention task and the latter requiring a selective attention task (60).

c. The Mismatch Negativity

The MMN is probably the auditory evoked potential that is currently the most investigated. It was described for the first time in 1978 by Näätänen et al. (61). It is elicited by any discriminable change in a repeated sound, even when the stimulus is not attended.
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Fig. 5
Schematic spectrogram of a consonant-vowel utterance showing the effect of changing the third formant (F3) transition trajectory on perception. The spectrogram is temporally aligned on the brief explosion of the consonant release, at which time, the spectrum shows a brief energy release across many frequencies. Voicing, the low frequency sound due to the vibration of the vocal cords is indicated by the vertical short thin lines. Voicing takes place 40 msec before the consonant release, thus signaling a pre-voiced consonant, indeed a /d/. Forty msec after the consonant burst, the vowel (an /a/) is in its steady state and can be identified by the relative position of its three formants. During the first 40 msec after the consonant release, there is a rapid modification of each of the three formants frequencies. These modifications are called formant transitions and their trajectories are crucial acoustic traits for consonant identification. In the example illustrated here, when the starting point of the third formant is 2580 Hz, the percept will be a /da/. If the starting point of the third formant transition is lowered to 2190 Hz, a /ga/ will be perceived.

make the MMN a credible candidate as a surrogate for the psychophysical measurement of discrimination thresholds since it provides precise feature-specific information on the accuracy of the central sound representation in the brain (67). The MMN is currently the only valid objective measure of the accuracy of central auditory processing in the human brain. It has already been used in this role to investigate primary acoustic dimensions like temporal resolution thresholds (70) as well as more complex, phonemic contrasts (71). It has also been shown by several groups that an MMN can be evoked in Cochlear Implant patients by the electrical stimulation of the eighth nerve (72-74). When elicited by simple, unidimensional (amplitude, frequency, duration or location of a pure tone) contrasts, the MMN can be used to assess unidimensional discrimination thresholds. When elicited by more elaborated stimuli, the MMN can reveal discriminations performed on the mental representation of the stimulus source, since it has recently been shown that it can be elicited by illusory percepts created by audiovisual interactions like the ventriloquism and the McGurk-MacDonald effects (75, 76). The McGurk-MacDonald stimulation paradigm offers a way to probe phonetic representations within the echoic memory without contamination by primary acoustic features. It has been suggested that a significant proportion of patients with CAPD probably have cortical rather than subcortical disorders and that therefore, the MMN might be the earliest neurophysiologic abnormality to be found (77). Measurement of the MMN might also demonstrate abnormalities in children whose primary defects are in the domains of learning or language rather than hearing (78). BALDEWEG et al. have (79) shown that dyslexic subjects have abnormalities in the MMN to changes in frequency but not changes in duration. The MMN can also be used to probe the relationship between CANS representation of speech sound and behavioral speech perception (7, 78, 80). We shall detail such one study (78) a little further in order to demonstrate what can be achieved by combining MMN recording and complex stimuli mimicking real-life speech sounds. Figure 5 depicts the schematized spectrogram of one of the consonant-vowel utterances used in (78).

In the example illustrated by figure 5, when the starting point of the third formant is 2580 Hz, the percept will be that of a /da/. If the starting point of the third formant transition is lowered to 2190 Hz, a /ga/ will be perceived. It is therefore easy, by controlling a single parameter of this complex signal, to evoke the perception of one or the other phonetic percepts. Several (i.e ten) intermediate values can be used in order to create a stimulus continuum allowing the psychophysical measurement of the discrimination thresholds or
Just Noticeable Differences (JNDs). By controlling the formant transition duration (from 10 up to 40 msec), another stimulus continuum is created, leading from the perception of a /ba/ to that of a /wa/. The first contrast is a spectral one, the second is a temporal one. Such contrasts have proved to be differentially disrupted in adults with central auditory lesions and children with auditory processing problems (71, 81-85).

In the study performed by Kraus et al. (78), it was found that within a population of children with documented learning problems, a subpopulation of them had greater JNDs than matched controls for the /da/-/ga/ continuum, but normal discrimination when tested with the /ba/-/wa/ continuum. The MMN recorded to the /ba/-/wa/ contrast was normal whereas it could not be elicited by the (not perceived) /da/-/ga/ contrast. Such results not only demonstrate the feasibility of using the MMN as a surrogate of behavioral testing, they also indicate that the basis for some speech discrimination difficulties may lie in deficits of neurophysiologic encoding along the auditory pathways. Interestingly, the same pattern of results has been found in age-related CANS dysfunction. Another example of how the MMN can be used to investigate central auditory code processing can be found in Winkler et al.’s study (87). These authors showed that the latency of the MMN evoked by stimuli that differ in term of ‘periodicity pitch’ is longer than that of the MMN evoked by an equivalent pitch change in pure tones. This is well in keeping with the notion that temporally encoded acoustic parameters need some incompressible processing time allowing the recognition of the temporal pattern of code (1), so that it takes longer for the cerebral process to extract pitch for periodic stimuli than for pure tones.

Although the MMN clearly possesses a tremendous potential for several clinical applications, it must be emphasized that under the current stimulation algorithms and recording techniques, its intersubject variability remains uncomfortably high in individual subjects (80). Although the evaluation of patients groups is quite feasible, it remains necessary to improve MMN stability and detectability across individual subjects if it is to be used on a single-patient basis (77).

d. P3

Discovered in 1965 (88) the P3 (or P300) component was rapidly associated with the stimulus that delivers relevant information in order to resolve the uncertainty preceding the correct identification of the target in a mixed sequence (89). Even an omitted stimulus can evoke a P3 component thus unequivocally demonstrating its endogenous nature (See figure3). Recent research led to the distinction between an earlier P3a with a more frontal localization and a later P3b larger over the parietal regions. P3a has been correlated with stimulus novelty and although it is attention-dependent, it does not require active patient participation. P3b is related to the task involved in the detection of the target stimuli and is significantly enhanced by active target identification (90). Many cortical and even subcortical regions contribute to the response. The P3 has been extensively studied in various pathological conditions ranging from attention deficits to diverse forms of dementia, with incursion into psychiatric disorders like schizophrenia. The amplitude of the P3 component has been reported to be abnormally low in a group of children with CAPD (51). Since P3 is influenced by attention, alerting, arousal, the subjects' psychological state and age, it is critical to establish norms for different conditions and to use stimulation paradigms and subjects' strategy monitoring that yield control over these numerous variables.

c. N400

Kutas and Hillyard (91) found that words ending sentences in an unexpected way (e.g. ‘I take my tea with sugar and cat’) evoke a negative component with a peak latency of 400 msec and a centro-parietal topographic distribution. This N400 component, which can be elicited either by an auditory input (92) or by a visual input (e.g. 91, 93), has mainly been used in order to study semantic aspects of speech (for a review, see (94)). There has been ample demonstration that the N400 is automatically evoked by semantic deviance, even though subjects do not pay attention to this particular dimension.

According to Kutas and Hillyard (91), the N400 wave would be an electrophysiological sign of the “reprocessing” of semantically anomalous information. In a subsequent study, the same authors found that the N400 amplitude increased as a function of the incongruity of the word. For example, in the case of the sen-
In the light of those few studies, we may conclude that the N\textsubscript{400} reveals, in real time, the activation of the neuronal systems in charge of semantic or phonological analysis of speech.

### Plasticity

The existence of a sensitive period during which human CANS plasticity progressively diminishes is a well-known issue that justifies major efforts in terms of early intervention for hearing loss. An emerging application of neuropsychology is to investigate the extent of various remedial strategies on neural code plasticity as evidenced by EPs modifications. One such study used synthesized speech stimuli delivered in quiet and in noise to evoke ABR and N\textsubscript{400} waveforms in children diagnosed having learning disabilities and/or attention deficit disorders. One subgroup was submitted to a remediation program incorporating exercises to improve temporal processing and phonological awareness skills. The other subgroup acted as a control for the effect of remediation. The results showed that, compared to controls, the remediated group exhibited changes in cortical responses in quiet and in noise. In quiet, cortical responses reflected an accelerated maturational pattern. In background noise, cortical responses became more resistant to degradation. ABR did not change with training. This training, which induced EPs plasticity evidenced at the cortical and not at the subcortical level, was accompanied by improvements in behavioral performances. In other studies using the MMN evoked by specific phonetic contrasts, it has been shown that training strategies based on enhancement of a temporal acoustic cue (lengthening of formant transition) did improve the MMN before improving behavioral discrimination (7, 80).

### Maturation

Age-related changes in the auditory EPs have been used to provide an insight into the maturation of the CANS, both in normal and auditory-deprived subjects (102-109). The matter appears to be quite complex and can only be briefly summarized in the context of the present review with reference to the relevant literature. Data accumulated up to now demonstrate at least four features of human CANS maturation:

1. **Maturation of the auditory EPs** extends well into adolescence and maybe even into early adulthood (109, 110). Moreover, it has recently been shown that the maturation pattern of the auditory EPs is dependent on the location of the recording electrode. To obtain a complete picture making it possible to decompose the recorded activity into its several components, it is necessary to perform dipole source modeling from extensive (typically around 30 or more) simultaneous scalp recordings (110). As to the MMN, it matures fairly early and has been shown to be, compared to N\textsubscript{1}, a better measure of basic auditory processes necessary for the development of spoken language perception skills in children and adults who use a cochlear implant (111).

2. **Maturation rates are not the same throughout the auditory system.**
3. Comparison of maturation rates for latencies of the different auditory EPs peaks indicates that this activity arises from parallel subsystems in the thalamo-cortical pathways. This is well in keeping with the parallel organization of the CANS as recalled in the introduction.

4. Generators or pathways contributing to a single evoked response peak may be distinguished by very different maturation rates. For example, the MLR peak P, appears to represent the sum of activity from two generators and two different pathways with very different maturation rates (105).

Conclusions

The progress made during the last decade in the neurophysiologic assessment of the human CANS has been quite significant. This is in great part due to the use of complex, more natural, mostly speech-like stimuli. Among the various types of potentials recorded, the MMN is rather unique since it is the only available neurophysiologic index of the accuracy of central auditory processing in the human brain. The extensive research efforts to which the present review has alluded to have contributed to a major improvement in our understanding of neural code processing by the CANS and have contributed to a better understanding of which process is going wrong in several patients' groups. Although some notable exceptions exist, it remains generally true that many research efforts and methodological improvements remain to be done in order to develop neurophysiologic tools able to diagnose a particular abnormality of processing or a given clinical disorder in individual patients. Nevertheless, there is little doubt that as progress is made, neurophysiologists will be more and more efficient in helping to distinguish between peripheral hearing problems, preconscious (MMN level) central sensory deficits and cognitive or language deficits. As already exemplified by some special patients' categories, it should then be possible to design fine-tuned remediation strategies for the benefit of clinical populations.

Discussion

The information yielded by EPs about how the CANS process the auditory neural code has obviously potentially powerful applications in the field of hearing loss, although, with a few notable exceptions, most of the literature reviewed in the present work falls outside this particular field. It is worth remembering that distortion of the peripheral neural is a frequent consequence of cochlear lesions (112) and that optimal remediation should aim at restoring a neural code that optimizes the identification of the sound sources. The several processing schemes and stimulation algorithms offered by cochlear implant devices as well as the wide possibilities of non linear processing provided by digital electroacoustic hearing aids allow an unprecedented level of flexibility in our ability to create or manipulate the peripheral neural code. There is little doubt that in the years to come, several of the neurophysiologic techniques described in this review will contribute to significant progress in this field too.

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Prof. P. Deltenre, M.D., Ph.D.
Clinique de Neurophysiologie
CHU Brugmann
place Van Gehuchten, 4
B-1020 Bruxelles, Belgium