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Possible Macroscopic Indicators of Neural Maturation in Subcortical Auditory Pathways in School–Age Children

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Abstract— **The examination of subcortical auditory processing by macroscopic electrophysiological measurements gains more and more interest in the group of school–age children, especially, in the objective diagnosis of the central auditory processing disorder. At the same time, recent behavioural and animal studies provided indicators for subcortical plasticity and neural maturation in auditory pathways in this age group. Therefore, it is important to examine which impact a possible neural maturation on subcortical large-scale electrophysiological diagnostic procedures has in this particular age. In this study, we compare auditory evoked brainstem responses of young adults and school–age children by a shift–invariant time–scale entropy as large–scale correlate of the neural group synchronization to an auditory stimulus. We found significant differences between these groups for binaurally evoked potentials under the condition of binaural fusion. It is therefore concluded that known difficulties in the evaluation of binaural interaction in children may stem from a neural maturation and increased plasticity.**

I. INTRODUCTION

The analysis of auditory brainstem responses (ABRs) represents a valuable diagnostic tool in the clinical practice. Beside well established diagnostic applications such as the objective detection of hearing thresholds in uncooperative young children, novel diagnosis techniques based on ABRs have recently been proposed such as the objective detection of central auditory processing disorder (CAPD) [1], [2], [3] or the machine based analysis of binaural interaction which might be useful for an objective fitting of cochlear implants [4].

Although numerous studies investigated the evolution of ABRs with age, this issue gains more and more interest with the exploration of the novel application fields mentioned before. Beside newborns as candidate group for objective diagnostic procedures, the group of school–age children is of increasing interest, e.g., for the objective diagnosis of the CAPD. Due to a comorbitity with other disorders such as attention deficit hyperactivity disorder, learning disability, and reduced intellectual functioning, subjective tests often suffer in CAPD diagnosis by extra–auditory factors such as reduced attention or a lack of cooperation [5] and objective tests using ABR analysis might be advantageous [6], [2].

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The studies on the age–dependent evolution of ABRs are usually based on the evaluation of conventional time domain features of the neural waveforms auch as amplitude and latency. Significant amplitude differences where found for normal hearing subjects at 1, 10, 30, 50, and 70 years of age (intragroup variation ± 6 months) in [7] but it is commonly believed that the morphology of ABRs in school–age children matches basically the adult waveform [8]. However recent studies have shown that there might be indicators for a subcortical plasticity also in the post preschool–age, e.g., in several animal experiments [9], [10], [11], [12], just to cite a few, in models [13], and very recently in a human study [14]. The authors in [14] showed that auditory training can alter the preconscious neural encoding of sounds by improving the neural synchrony in the auditory brainstem.

It is the aim of this study to evaluate whether there are qualitative and quantitative neural correlates of a brainstem plasticity in monaurally and binaurally click evoked ARBs of school–age children using more advanced techniques of signal processing than a conventional assessment of time domain features. In particular, we apply a shift–invariant time–scale entropy analysis of ABRs for the quantification of the neural group synchronization due to the auditory stimuli.

II. METHODS

A. Patients and Materials

The whole study group of 40 subjects can be separated in one group of 20 school–age children (age: 7 to 9 years, mean age: 8.3 years) and a reference group of 20 young adults (age: 18 to 23 year: mean age: 21.6 years). These reference group of rather young adults was chosen as in older adults other factors than the plasticity might heavily influence the results [7].

All subjects have a normal hearing (threshold <10dB HL between 0.5kHz and 6kHz) without any history of CAPD and without intellectual deficit. Normal directional hearing was verified using a localization test in a setting where 7 sound sources were located in a half circle around the patient. Measurements of binaural intelligibility level difference using a commercially available test (BIRD–Test, Starkey Laboratories, Germany) were applied to prove a normal signal detection in noise. In all subjects, the wave V latencies in the monaural responses differed not more than 0.2ms. Thus binaural interaction is expected being present in the whole study group.

Auditory evoked potentials were obtained using a modified commercially available device (ZLE–Systemtechnik,

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Munich, Germany) in a sound proof chamber. In each measurement, 4000 alternating clicks were presented binaurally or monaurally at an intensity of 65dB (HL) with an inter stimulus interval of 60ms. In the binaural measurements, the interaural time delay (ITD) (stimulus on the left side being delayed) varied between 0.0 and 1.0ms (0.0ms, 0.4ms, 0.6ms, 0.8ms, 1.0ms). Two monaural measurement were carried out at a stimulus intensity of 65dB on the left and on the right ear, respectively, with masking noise presented on the contra–lateral side at an intensity of 45dB (HL).

The potentials were recorded using electrodes placed at the neck, the vertex and the upper forehead, respectively. Electrode impedances were below 5 kΩ in all measurements (filter: 0.1kHz–5kHz, sampling frequency: 20kHz, amplification factor: 150000).

There was no significant difference between the two groups of subjects regarding the number of produced artifacts, impedance as well as the signal–to–noise ratio such that the very same measurement quality can be assumed for both groups.

B. Time–Scale Entropy

There are several different applications for the entropy concepts. Here it is most appropriate to consider the entropy simply as a measure of disorder of a system or process. ABRs are due to neural group synchronizations of the spontaneous brain activity. This can be seen as a transition from a disordered state (the spontaneous activity) to an ordered state (the neural response upon the auditory stimulation). Consequently, an entropy measurement of time series seems to be promising for the analysis of ABRs and the quantification of the neural synchronization represented by EEGs, see [15].

The *spectral entropy* [16] derived in the Fourier domain has been applied to EEG signals in [17]. Recently, entropy measurements based on wavelet decompositions have been proposed for the analysis of EEG signals, the so–called *wavelet entropy* [15]. Since EEGs are usually nonstationary signals, such an analysis concept which provides locality in time is clearly more appropriate than the spectral entropy. Of course, the spectral entropy can also be applied for an analysis which provides locality in time by the windowed Fourier transform, see [16]. However, the wavelet transform has the advantages which we have discussed earlier, i.e., a variable analysis window in the time–frequency domain and a flexible choice of the basis functions. Therefore, entropy measurements based on wavelet decompositions seem to be preferable to those derived from the windowed Fourier transform.

The entropy information derived in the wavelet domain has very recently been applied for the analysis of event related evoked responses and has shown to be not trivially related to the signal energy and thus not the signal amplitude, see [15].

In [15] orthogonal wavelet decompositions based on two channel maximally decimated paraunitary filter banks were used for the entropy measurements. However, such orthogonal decompositions are strongly shift–variant [18] and a minimal shift of the signal to be analyzed results in a significant redistribution of the energy induced in the individual octave bands [18] which also changes the entropy. Therefore, we prefer a definition of the *scale entropy* and the *time–scale entropy* from the continuous wavelet transform which provides a high resolution and shift–invariance, improving the analysis, see [2].

Let $\psi_{a,b}(\cdot) = |a|^{-1/2}\psi((\cdot - b)/a)$ where $\psi \in L^2(\mathbb{R})$ is the wavelet with $0 < \int_{\mathbb{R}} |\Psi(\omega)|^2 |\Psi(\omega)|^{-1} \mathrm{d}\omega < \infty$ ($\Psi(\omega)$ is the Fourier transform of the wavelet), and $a, b \in \mathbb{R}$, $a \neq 0$). The wavelet transform $\mathcal{W}_\psi : L^2(\mathbb{R}) \longrightarrow L^2(\mathbb{R}^2, \frac{\mathrm{d}a\mathrm{d}b}{a^2})$ of a signal $x \in L^2(\mathbb{R})$ with respect to the wavelet ψ is given by the inner L^2–product

$$(\mathcal{W}_\psi x)(a, b) = \langle x, \psi_{a,b} \rangle_{L^2}. \qquad (1)$$

.

In this study, we used the 6th–derivertive of the Gaussian function as wavelet, see [19]. For analyzing a sampled ABR waveform $s \in \mathbb{R}^d$ (d is the number of samples) by (1) instead of continuous functions, we introduce the following discretization. Let us define the sampling spaces $\mathcal{A}$ and $\mathcal{B}$, respectively, which are associated with uniquely sampled intervals $[a_l, a_u]$ and $[b_l, b_u]$ ($a_l, a_u, b_l, b_u \in \mathbb{R}_{>0}$) of the scale and the dilation parameter, respectively. The sampled version of the corresponding wavelet transform is denoted by $(\mathcal{W}_\psi s)[m, n]$ ($m \in \mathcal{A}, n \in \mathcal{B}$, $s \in \mathbb{R}^d$) in the following.

For a given ABR waveform s, we define the (time dependent) scale entropy by

$$E_s[n] = -\sum_{m \in \mathcal{A}} g[m, n] \ln g[m, n] \qquad (2)$$

where

$$g[m, n] = \frac{(\mathcal{W}_\psi s)^2[m, n]}{\sum_{i \in \mathcal{A}} (\mathcal{W}_\psi s)^2[i, n]}.$$

The global time–scale entropy is defined by

$$E_s^\epsilon = \sum_{m \in \mathcal{A}} \sum_{n \in \mathcal{B}} e_s^\epsilon[m, n] \qquad (3)$$

with

$$e_s^\epsilon[m, n] = \begin{cases} k & \text{for } |(\mathcal{W}_\psi s)[m, n]| > \epsilon \\ 0 & \text{else} \end{cases} \qquad (4)$$

where $k \in \mathbb{R}_{>0}$. Note that the functional in (2) is also the well known Shannon entropy [20] of a finite scheme but one where the probabilistic events are replaced by normalized energies of the samples, i.e., we do not deal with the probabilistic concept of the entropy here. Such a normalized entropy has been introduced in [21] purpose of signal compression.

III. Results

In Fig. 1 we have shown an ABR after binaural stimulation for an increasing ITD (left column) for an adult as example. The corresponding time–scale representations are shown in the middle column and the time dependent scale entropy analysis in the right column. It is noticeable that for smaller

ITDs the energy of the waveforms is concentrated in smaller scales (the brighter the points, the larger the absolute value). For an ITD of 0.0ms, the largest part of the energy is induced for $a \in [25, 35]$ for all subjects included in our study. For an increasing ITD, the concentrations 'dissolve' towards larger scales. This effect is directly reflected in the scale entropy analysis. The wave V of the response corresponds to the largest neural group synchronization and reduces the scale entropy crucially for smaller ITDs. For ITDs larger than 0.6ms, the entropy increases. In [2] it was shown that from the resulting less structured waveforms is very difficult to derive a stable β–wave as correlate of binaural interaction in the binaural interaction component, i.e., the difference between the sum of the monaural waveforms and the binaural waveform.

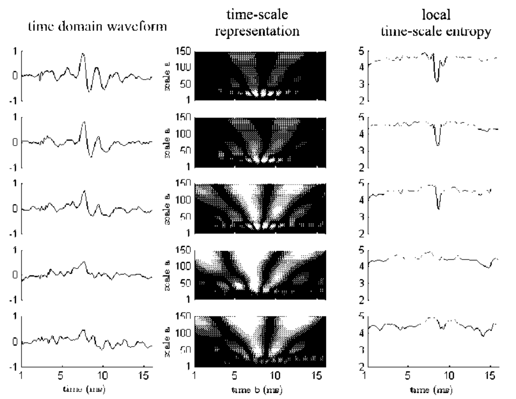

Fig. 1. An ABR with a pre–stimulus interval of 2ms for different ITDs (left column) for an adult. The corresponding absolute values of the time–scale representation are shown in the middle column. The scale entropy E_S is shown in the right column (increasing ITD from the top row: 0.0ms, 0.4ms, 0.6ms, 0.8ms, and 1.0ms in the plots at the bottom row).

In Fig. 2 the local entropy of a binaural ABR is shown for child. It is clearly noticeable that the entropy is rather large for smaller ITDs compared to the young adult subject in Fig 1. Thus the increase is less significant between a fused image of the binaural stimuli and for larger ITDs when morphologies reflect rather the spontaneous activity than highly synchronized neural activity.

To examine the entropy differences between both groups, we apply the global time–scale entropy. For these examinations, we set $k = \sqrt{m}$ in (3). In this way, we obtain a weighted threshold entropy which takes the concentration at smaller scales and its disintegration towards larger scales for an increasing ITD into account, see Fig. 2 (middle column). We use a threshold ϵ equal to 35% of the maximal absolut value of the transform in (4).

In Fig. 3 we have shown the mean of the weighted threshold entropy for the 40 subjects for the binaural waveform and the sum of the monaural waveforms. For this investigation, we have reduced the time interval to [3ms, 9ms] to set the focus tighter on the information of wave V, i.e., the most prominent wave in ABRs. It is clearly noticeable that the averaged entropy increases crucially with the ITD in the binaural waveform as well as in the sum of the monaural responses. As the entropy increases in both waveforms, this behaviour cannot be denoted to binaural processing but is just a consequence from the fact that the neural responses become more and more decorrelated. There is a significant (Wilcoxon–test, $p < 0.05$) difference between the group of children and adults for ITDs smaller than 0.8ms. The larger group synchronization for smaller ITDs is more prominent in the group of adults than in the group of children.

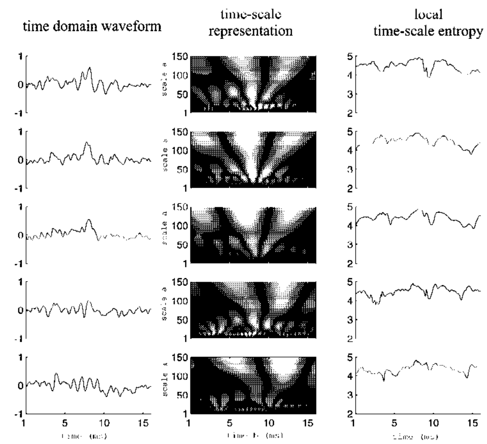

Fig. 2. An ABR with a pre–stimulus interval of 2ms for different ITDs (left column) for a child. The corresponding absolute values of the time–scale representation are shown in the middle column. The scale entropy E_S is shown in the right column (increasing ITD from the top row: 0.0ms, 0.4ms, 0.6ms, 0.8ms, and 1.0ms in the plots at the bottom row).

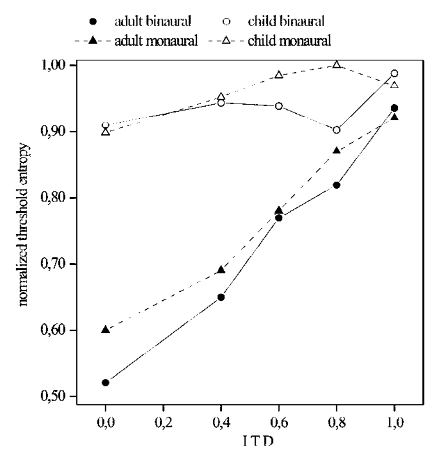

Fig. 3. The threshold entropy (mean) for different ITDs (normalized scaled) for both groups after binaural and monaural simulation (shown is the analysis of the sum of the monaural signals). The standard deviation was below 0.37 for all ITDs in both groups

IV. Discussion and Future Work

It is commonly believed that the morphology of ABRs in school–age children matches basically the adult waveform [8]. However, our study showed that there are differences between a group of children and young adults regarding the time–scale entropy of ABRs which can be considered as a large–scale measure of the neural group synchronization. These differences were significant for ITDs smaller than

0.8ms where we expect a large group synchronization. In other words, the subcortical auditory paths in the group of adults seem to be more consolidated as in the group of children which seem to exhibit a neural maturation at this level.

In the design of our study, we made sure that there were no other significant differences in the signal–to–noise ratio, number of artifacts, and impedance between the different group such that the very same measurement quality can be assumed.

Or results are in accordance to recently found indicators for a subcortical neural maturation and plasticity in school–age children using animal experiments and [10], [11], [12] and due to neurophysiological measures after pre– to post auditory training in this age–group [14]. Also computational models reflect this hypothesis [13].

A large entropy corresponds to less structured waveform which is more difficult to analyze as shown in [2] for the β–wave detection in binaural interaction component for larger ITDs. Therefore, our findings are significant for the development and evaluation of diagnostic procedures on the subcortical level using large–scale electrophysiological data in school–age children. This is especially important for the objective detection of CAPD in this age group. In [3] a hybrid detection paradigm has been introduced for the objective detection of CAPD in school–age children using robust kernel classifiers and tailormade feature extractors on ABRs signals. Our result underline again the importance of the use of such robust schemes instead of simple time domain features which may be unstable and fragile in this particular age group.

The entropy measure introduces here is based on averaged data. We are currently collecting a single sweep, i.e., the response for an individual stimuli, database of adults and school–age children for the further ABR analysis as in [22] using different stimulation paradigms. This may help to identify the origin of the large entropy in ABRs of children using time–scale coherence measures [23].

V. Conclusions

It is concluded that there are possible macroscopic indicators of neural maturation in subcortical auditory pathways in school–age children using the described ABR time–scale entropy analysis. The presented results are significant for the development and evaluation of objective diagnostic procedures in this age group using large–scale electrophysiological data from the brainstem level. Further work may consist in a single sweep analysis of ABRs to identify the origin of the increased ABR entropy in children as reflected in the averaged responses.

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