Key words: CAPD, Auditory Event Related Potentials (AERP), Contingent Negative Variation (CNV), LASER, attention problems, respiratory chain, ATP, Wire and Fire, Learning disabilities

Hypothesis for a future application of a Laser-device in patients with symptoms of a developmental auditory processing disorder. Part II: Evaluation of clinical cases.

E. Friederichs
Centre for Development and Learning, Bamberg
Business and Economic Education, University of Bamberg, Germany

ABSTRACT

The present study examined whether changes of electrophysiological late event related potential pattern could be used to reflect clinical changes from therapeutic intervention with a LASER-device in a group of patients with symptoms of central auditory processing disorder (CAPD). The contingent negative variation (CNV) and event related auditory cortical potentials (AERP) reflect a synchronization of together firing wired neural assemblies responsible for auditory processing, suggesting an accelerated neuromaturation process when applying a LASER device stimulation. This was discussed already in Part I of this article (1), where a model was presented explaining possible effects of LASER application of auditory neurons by inducing the respiratory chain of the mitochondria. Part II of the article now provides clinical data, that a LASER stimulation might be useful for the clinical improvement of attention (distraction) symptoms caused by auditory processing deficits.

Subjects consisted of 59 patients average age 14 years (range 7-53 years) with normal hearing threshold, learning disability and attention deficits caused by central auditory processing disorder. These patients were stimulated with a LASER-device system. Results after 10 LASER stimulation sessions indicated, that this type of LASER-device stimulation significantly improved auditory CNV and p200/p300 pattern morphology.

INTRODUCTION

It is well accepted that an acoustical environment (noise and reverberation) in classroom conditions is a critical factor in the educational achievement of many children. Such populations being at risk for academic failure encompass children with language impairment, dyslexia, attention deficits and general developmental delay (literature in 1). It is reasonable to assume, that poor neural acoustic representation will lead to serious problems in the maturation of the auditory pathways and hence the development of auditory process ability. Recent research suggests that neuroplasticity and neuromaturation are dependent on stimulation (11, 12). Therefore comprehensive management of CAPD should include auditory stimulation to achieve functional changes within the central auditory nervous system. Thus young children would be expected to benefit from a great degree of neuroplasticity. In another paper (2) we focused already on the use of late event related auditory potentials (AERP´s) in documenting changes in clinical status after direct stimulation with binaural FM-devices. These data were interpreted as indicating that neuroauditory maturation could be influenced by a specific intervention and could be distinctly objectified by means of late event-related potential measures.

Recording of the Contingent negative variation (CNV) and p200/p300 pattern requires the patient to pay active attention to a stimulus. Auditory event related potentials (AERP´s) allow the evaluation of brain activities and are presumed to be related to attention, recognition, and memory processes. The contingent negative variation (CNV) is a slow negative potential decrease, which will appear hundreds of ms before target stimulation. CNV is representing a large number of increasing synchronous self

regulatory excitatory activity of neuron populations and is preparing the brain for the following auditory stimulus. In this sense CNV and p200/p300 are related to the synchronous firing of wired neurons in order to provide the ability of reaction capacity of a certain brain task.

Studies of brain development show that sensory stimulation in the case of the visual centres of the brain is critically important, and influences the actual organization of visual brain pathways. Increase in visual stimulation results in morphological and functional alterations within the visual parts of the brain (4, 5). Strategies for stimulation of auditory processing disorder are usually direct remediation, environmental modifications and compensatory strategies. One of a possible new strategy for reducing the deleterious effects of auditory noise is the use of LASER light, providing discrete wavelengths (frequencies) to improve auditory clarity and avoidance of ear pressure, tinnitus and background noise (2,8). The purpose of direct stimulation of auditory processing on the level of neurostimulation is to maximize neural plasticity and possibly accelerate maturation, improving auditory performance.

The purpose of this article is to present data from patients with developmental auditory-perception problems when applying LASER light. A hypothetical model is already discussed in Part I of this article (1) to explain the results using electron modelling and proton exchange inside the respiratory chain. As this article is the second part of a two-part article it is referred to the first part for reasoning of this clinical evaluation. Most of the literature is already cited in Part I of this article (1).

METHODS

Subject selection criteria

59 subjects (47 males, 12 females) with normal hearing sensitivity participated in this study. Subject age ranged from 7 to 53 years with a mean age of 14 ± 10 years.

All subjects met the following criteria: Hearing sensitivity better or equal to 20 dB HL at 250 – 8000 Hz, German was the primary language. All subjects had a history of learning disability and attention deficits. 13 patients were additionally diagnosed with ADHD by DSM IV criteria and well controlled treated with stimulant medication. In these cases CAPD was considered as a comorbid condition of ADHD. Children with and without ADHD did not demonstrate a significant different distribution pattern of pathological auditory event related potential. This is in agreement with other literature (7). Only subjects were included with an IQ-level ≥ 90 measured with different appropriate instruments.

All subjects were administered with electrophysiological tests before and after 10 sessions of LASER stimulation 1 - 3 months after LASER stimulation.

Assessment battery

Prior to participation in the study each subject underwent a comprehensive audiologic evaluation to rule out any abnormalities of the auricle and auditory meatus. Pure tone air and bone conduction thresholds were assessed using a Maico ST-28 clinical audiometer (250-8000 Hz) demonstrating normal values. Tympanometry and acoustic reflex as well otoacoustic emission testing revealed normal values. All subjects were required to have normal ABR tracings in each ear.

Laser application

The Laser source was a Multiwave Locked System Laser (MLS®, ASA Srl, Vicenza, Italy). It is a commercially available laser source built in compliance with EC/EU rules, which received FDA clearance and is widely used in clinics. MLS® laser is a class of NIR laser with two synchronized sources (laser diodes). These emit at two different wavelengths, peak power and emission mode. The pulse frequency is for both wavelengths 1500 Hz (T-on mode) delivered to the auditory neurons. The first one is a pulsed 905 nm laser diode with 25 W peak optical power with a pulse duration of 100 ns. The second laser diode (808 nm) is operating with 1000 mW optical power with a pulse duration of 300 µs. The two laser beams are emitted synchronously and the propagation axes are coincident. The patients received the following energy dose on both ears for 1/2 hour separately: 164.43 J/cm^2 (according to A. Kaiser, personal communication).

Event Related Auditory Cortical Potentials (AERP)

Cortical potentials were recorded from 26 electrodes positioned on the human brain scalp according to the international electrode placement system (10-20). To maximize CNV, P200 and P300 amplitudes and stability, electrodes over the central (CZ, FZ, PZ), left (C3, F3, P3, F7, T3, T5, P3, O1) and right (C4, F4, P4, F8, T4, T6, O2) central, parietal and occipital cortex parts of the brain were used for evaluation.

Electrodes were referenced to linked earlobes. Vertical EOG provide control for blinks. Data were recorded with a 32–channel bio signal amplifier (Brainamps) with a frequency response 0.5 to 30 Hz and a A to D conversion rate of 1000 Hz. Trials were corrected for baseline and VEOG artefacts with the brain vision analyser software. These data were interpreted as indicating that neuroauditory maturation could be influenced by a specific intervention and could be distinctly objectified by means of late event related potential measures.

Auditory CNV (contingent negative variation):

Recording of the CNV potentials was

achieved by presentation of 50 tone burst sequences (25 high frequency/ low frequency 3 kHz/2 kHz and 25 low frequency/ high frequency 2 kHz/3 kHz tone burst sequences, 75 dB HL), respectively. Stimulus duration was 50 ms. The Interstimulus Interval (ISI) is offered with 5 sequences of 10, 20, 30 40 or 50 ms. Mean reaction time and number of errors of omission and commission were recorded separately (not shown). 1.5 seconds prior to the burst sequences a warning burst tone (1 kHz, 15 ms duration) was presented. Prior to recording the event related potentials subjects were given time to practice the tone discrimination task to become familiar with the paradigm while listening to the high/low frequency tone burst sequences presented. According to the number of errors of omission the ISI intervals were adapted to 50, 100, 150, 200 and 250 ms, respectively. Subjects were asked to answer either with "high" or "low" after the second tone burst was realized.

CNV reflects a slow potential drift towards negativity, which will take place several hundreds of ms before target condition, preparing the processing of the following target stimulus. One CNV epoch was scored separately for tone burst (target) trial from all electrode positions. From 1120 ms on before target stimulus, a significant CNV component can be detected, representing an excitatory activation of the corresponding brain area.

Auditory P200 and P300 components:

Recording of the potentials was achieved by presentation of frequent and infrequent tone bursts (75 dB HL) at a ratio of 3:1 in an "oddball paradigm". The children were asked to recognize the infrequent stimuli. Binaural tones were presented in a random sequence with a 2.2 kHz infrequent target tone and 4 kHz frequent target tone with a stimulus duration of 50 ms and an ISI of 3025 msec. Prior to recording the event related potentials subjects were given time to practice the tone discrimination task to become familiar with the oddball paradigm while listening to the rare and frequent tones presented. Each session consisted of 75 presentations of the frequent tone and 25 presentations of the rare tone in a random sequence. Subjects were asked to push on a mouse button whenever an infrequent tone was realized.

Latency and amplitude measures were averaged over three complete trials for the N1, N2, P2 and P3 components of the long latency response to the target tone. P2 was identified as the largest positive peak between 130 and 290 ms, following N1. P3 was identified as the highest positive peak between 250 and 600 ms following N2. Latency was measured to the highest peak on the wave. Amplitudes were measured at the highest wave peak relative to the prestimulus baseline: Artefact rejection was set to ignore any trial which the ongoing EEG exceed ± 140 µV. Averaging was carried out generally over all segments allowing comparison among several data sets with the same software.

This method (P300 "oddball paradigm") was specifically selected. In this case a series of paired stimuli has to be detected

Figure 1 - Composite Grand Mean CNVs before (red) and after (green) LASER application.

which reflects additionally aspects of attention, discrimination and memory.

Laboratory analysis

ATP levels were determined in an outsourced laboratory. Mitochondria are compartments of eukaryotic cells. They produce by means of the respiratory chain using oxygen, glucose and phosphate ATP. ATP determination is provided by measurement of the ATP production in mitochondria from living T-lymphocytes of the patient. Cells with adequate ATP production show after addition of a specific metabolic agent a different color spectrum compared to cells with decreased ATP production. Differentiation and quantification take place in a high sensitive fluorescence-activated cell sorter.

Statistical analysis

Statistical analysis was done with a temporal resolution t-Test belonging to the Brain Analyser software system. All analyses were performed at a $p < 0.05$ level of significance.

RESULTS

Electrophysiological results

CNV

Composite grand mean wave forms for the experimental groups at different time intervals are shown in Figure 1. The two waveforms represent the CNV locations in target condition (red: inital situation; green: after 10 binaural LASER sessions). Notice in the development of the CNV distribution pattern the increase in CNV area from the frontal to the parietal electrodes already after 10 LASER application sessions. A map view of CNV between the time interval – 300 ms to 0 ms (appearance of target stimulus) illustrates the increase in excitatory activation of neuron population after the course of 10 sessions of LASER device applications (Fig. 2 before and Figure 3 after LASER application). Table 1 shows the mean values of absolute CNV areas under curves calculation levels before and after 10 LASER applications, respectively.

Figure 2 - Composite Grand Mean CNVs (mapping view -300 ms to 0 ms) before

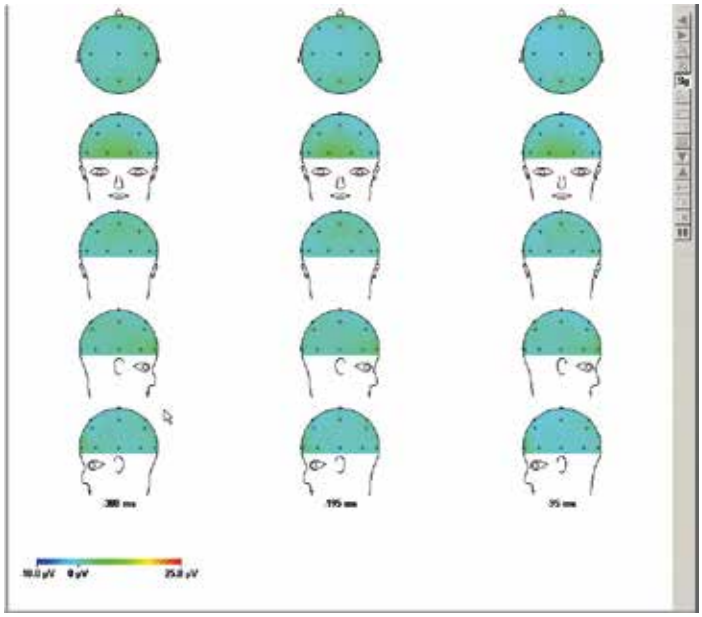


Figure 3 - Composite Grand Mean CNVs (mapping view -300 ms to 0 ms) after

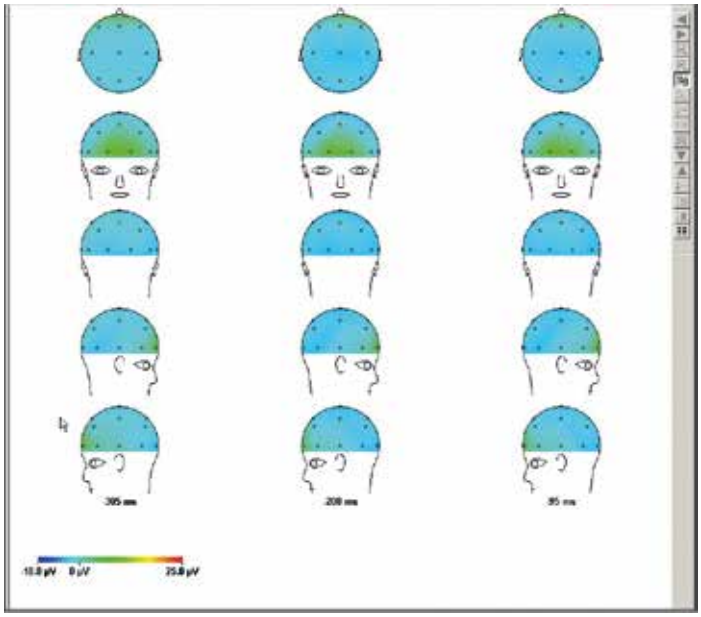


Figure 4 - P200/P300 Pattern (before)

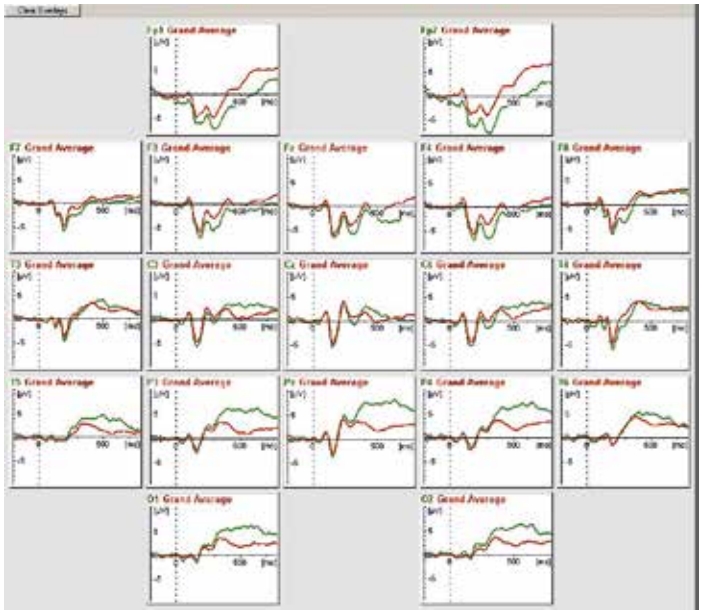


Figure 5 - P200/P300 Pattern (after)

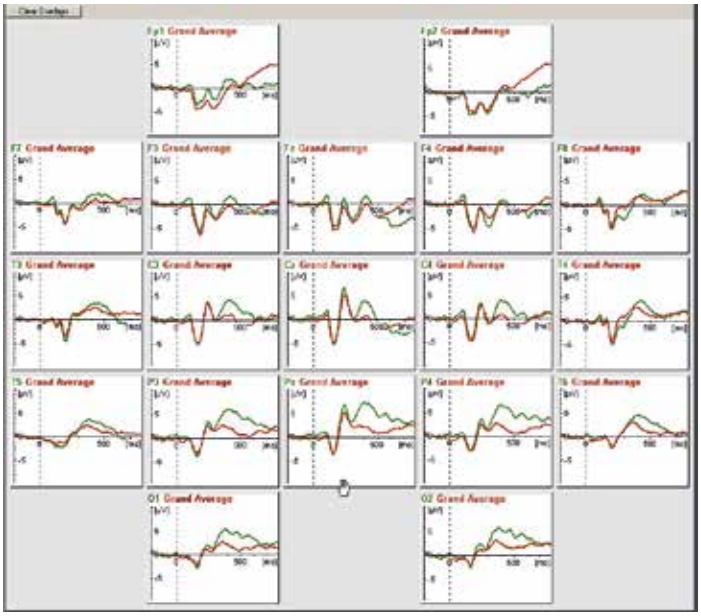


Figure 6 - C3,C4,Cz left, right and central electrode sites (before)

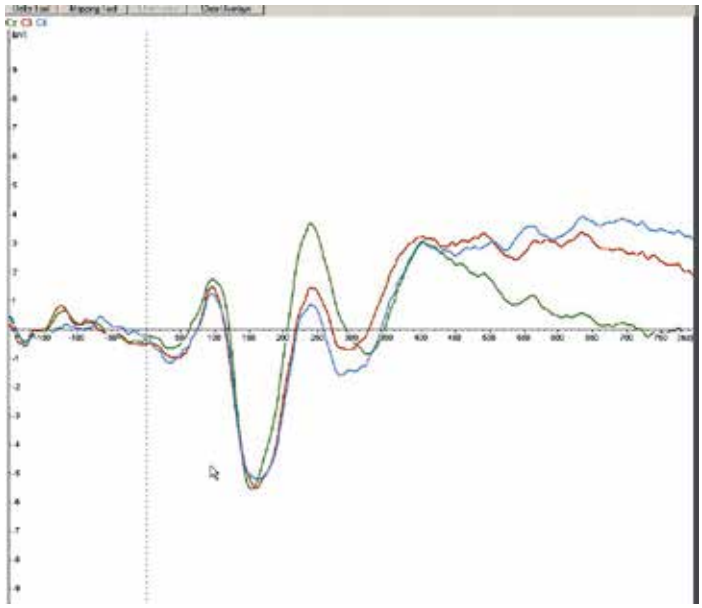
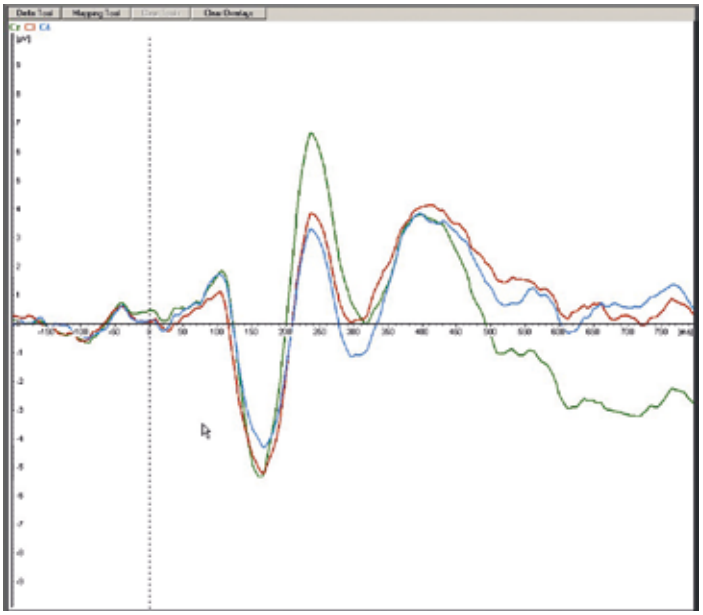


Figure 7 - C3,C4,Cz left, right and central electrode sites (after)



P200/P300

Analysis of the P200 and P300 components reveals a significant height and morphological discrepancy between the target condition (green line) and the non-target condition (red line) after the LASER application (Figure 5) compared to the inital situation (Figure 4) level reflecting an increased discrimination efficiency especially at the P300 level.

Composite grand mean wave forms for the experimental groups at different time intervals are shown in Figures 6, 7, 8 and 9. The three waveforms represent in Figure 6 the C3 (red), C4 (blue), CZ (green) and in Figure 8 the P3 (red), P4 (blue) and PZ (green) non-inverting locations before LASER application, while in Figure 7 and 9 the appropriate locations are shown after 10 sessions of LASER application. Notice in the case of infrequent tone responses the development of the classical P200/P300 distribution pattern with increase in P200 amplitude and more pronounced P300 pattern after LASER application reflecting an improved allocation of resources.

Table 1 shows the absolute PZ amplitude mean values. It should be noticed that the P3, P4, PZ pattern of the treated sample approached more pronounced waveform pattern after LASER application compared to the initial pattern giving a more convincing argument than only looking at the absolute PZ levels.

Table I - Pre- and post treatment mean area (μV*ms) and amplitude (μV) and latency (ms) measures for P200 and P300 of the patients taken from the graph

	CNV (CZ) Area (μV*ms)		P200	P300	P200	P300
			Peak height (μV)		latency (ms)	
Before	190	p <	4.84	7.22	240	400
After	4277	0.05	6.62	7.12	240	400

Figure 8 - P3,P4,Pz left, right and central parietal electrode sites (before)

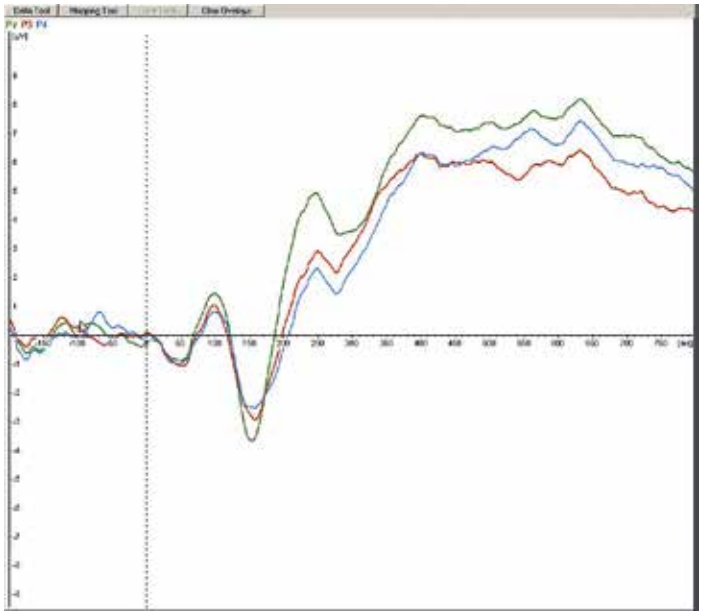
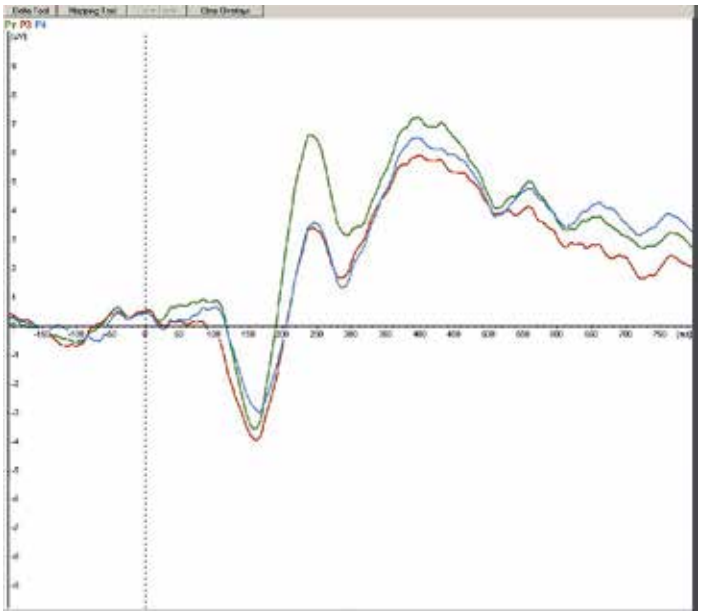


Figure 9 - P3,P4,Pz left, right and central parietal electrode sites (after)



ATP levels

ATP levels before and after intervention (% T cells):

Before	After	p
92.8 +/- 11.6	98.8 +/- 1.8	< 0,05
Range 46 - 100	95.0 – 99.9	

ATP levels before and after intervention were significantly different, reflecting a possible energy dependent reaction.

DISCUSSION

Only a few studies have been found in literature having focused on the use of CNV and P300 potential in documenting changes in clinical status (literature in 1). This study was designed to evaluate whether development of the event related auditory event related potential distribution pattern would reflect any changes of the auditory processing system resulting from LASER stimulation. Recording of the CNV requires the patient to pay active attention to a stimulus. AERP´s are presumed to be related to attention, recognition, and memory processes. Our results revealed a significant improved allocation of resources of patients with CAPD after 10 LASER stimulation sessions. This is reflected in the differential reaction on relevant and non relevant stimuli measured with the P200/P300 pattern as well as in CNV pattern before and after the course of 10 LASER stimulation sessions.

Although some of the electrophysiological changes might be attributable to normal maturation processes, the differences in CNV distribution pattern and P200/P300 from the pre-and post measures can be assigned to the treatment intervention. This can be interpreted as precise discrimination efficiency and as an optimization of the central auditory information processing. The improved activation pattern of the contingent negative variation (CNV) can be explained by a synchronous activation of a great amount of neurons population (assembly) which are necessary to prepare for course of action.

The organic living brain is quite the opposite of an engineered machine with hardwired circuits that can only perform a limited number of actions, but during the day the brain is forming / uniforming new flexible neuronal networks. A group of neurons will be used for different purposes at different times. Tasks can be performed using different coalitions (assemblies) of neurons (4, 5). Learning skills are encoded in the cumulative electrical patterns resulting from the neurons firing together (4, 5). The pattern, i.e. the population is interesting, not the individual cell. Cells that are, on whatever reason, chronically inflamed, are more sensitive to red and near-infrared light than are well-functioning cells. To heal, the body often needs to create new cells. The first step in cell reproduction occurs when DNA replicate itself. Specific wavelengths 404, 620, 680, 760 and 830 nm can activate DNA and RNA synthesis in cells by inducing the respiratory chain of sick neurons thus leading to an increased cell proliferation (literature in 1).

Wilden et al. (8) already reported, that LASER stimulation with distinct wavelenght may vitalize the cell by increasing the mitochondrial ATP (adenosine-tri-phosphate)-production. With regard to radiation phenomena and its inhanced electron flow in the cellular energy transfer (respiratory chain), these authors postulated already that the experimentally found increase of ATP-production could be explained by means of low-level laser light on a cellular level. Their investigations are mainly based on patients with Tinnitus and sudden hearing loss, while developmental hearing problems are not considered. Our data support this hypthosesis as ATP concentration significantly increased after LASER application. The model is extensively discussed in Part I of this article (1).

In most of the patients the CNV before LASER stimulation was abnormally evoked, severely reduced and in most of the cases absent in amplitude suggesting problems of the patients paying attention. As CAPD can be a distinct disorder or a comorbid condition of ADHD the success of this type of intervention seems to be independent of the type of CAPD: Children and adolescents applied with LASER stimulation did significantly and in different degrees benefit from this therapeutic approach whether ADHD was present or not. It seems reasonable to assume that changes in the amplitude and/or morphology of the P200/P300 waveforms correlate with changes of the clinical status.

Because maturation processes in highly plastic brains in childhood should be enhanced through sensory stimulation, expectation of improvement of auditory processing abilities could be confirmed in the current investigation. These findings support previous research from our group showing that children with various types of learning or cognitive disorders may be (i) differentiated from normal control subjects on the basis of event related potentials and (ii) stimulation by FM-devices could indeed improve auditory processing abilities (2). Data of the control subjects from this study could serve as a baseline definition. While trainings or FM-devices usually will be applied in the morning or the afternoon as additional educational support for the children, LASER stimulation can be applied independently from school schedule and may have a faster and a more sustainable success for the disabled children. Because auditory neuromaturation and

neural plasticity depend on distinctive auditory stimulation, "aggressive" management of CAPD (either with or without ADHD) should begin as early as possible. Studies of brain development show that sensory stimulation of the auditory centres of the brain is critically important, and influences the actual organization of auditory brain pathways (9). Increase in auditory stimulation may result in morphological alterations within the auditory parts of the brain (10, 13). The ability of the auditory cortex to reorganize continuously throughout life span reflects the ability to acquire new skills and behaviours. Several studies have focused on the use of the late auditory event-related potentials (AERPs) in documenting changes in clinical status. These studies emphasized the feasibility of using P300 event related potentials to document levels of auditory dysfunction (14, 15). There are several studies suggesting that P300 auditory event related potentials in children with CAPD showed longer latency times and smaller amplitudes compared to controls (16,18,19). Jirsa (16, 17) demonstrated a significant decrease in P300 latency time along with an increase in P300 amplitude in the evoked potentials obtained from children with CAPD following an intensive therapeutic 14 week intervention program. The children in the experimental group exhibited improvement on selected auditory tasks and positive changes in overall academic performance. These data were interpreted as indicating that neuroauditory maturation could be influenced by a specific intervention and could be distinctly objectified by means of late event related potential measures. In our case, no decrease in p300 latency time could be demonstrated. One explanation might the difference in maturation stage from our subjects, as the age range of our subjects was from 7 to 53 years. Further studies (including longterm follow up) have to address the question whether use of AERP´s may be more sensitive for prediction of treatment outcomes as it has been already suggested by Walsleben et al. (6). Studies on AERP measures performed at different maturation stages and with increased number of LASER simulation sessions are in progress, to predict already possible therapeutic advantages of such a LASER device very early. The degree and speed of improvement between different forms of interventions has still to be evaluated.

Although results of this type of investigation must be interpreted cautiously because of the limited number of subjects and possible interfering medication effects, they do suggest that event related potential measures are sensitive to changes in clinical status when applying a controlled use of LASER stimulation in children/adolescents with CAPD. Up to now there is still a great lack of consensus on precise definitions of what a processing disorder encompasses. It is not yet clear how to differentiate a CAPD from other processing disorders. Future research has to address these questions to enhance specifity of the clinical intervention tools and/or programs on auditory neuromaturation. Additionally it can improve our knowledge of the development of auditory function in children. Intrahemispheric and interhemispheric functional measurements may also give a more precise view into these questions. In summary our data support, that auditory event related potentials measures may be useful in the clinical assessment and treatment of populations with possible CAPD. Maturational effects cannot be totally excluded, but are not expected already after 3 to 4 months. Further research is warranted. Thus, our data support (a) the use of electrophysiological measures as a more sensitive parameter for the detection and follow up of auditory neuromaturation processes which was (b) induced by LASER stimulation.

Use of LASER stimulation does not replace other intervention measures as occupational therapies or other kinds of auditory training interventions although they may support and possibly accelerate these methods. In some cases LASER stimulation might not be helpful. As a result of this clinical evaluation patients and their parents need to be intensively involved in the decision making process using a LASER device very early to improve acceptance and the beneficial effect of such a tool.

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Conflicts of Interest

The author declares that he discloses any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

All inquires should be directed to:

Prof. Dr. Edgar Friederichs
Centre of Development and Learning
D-96047 Bamberg, Germany
Phone: (+49 951) 297 299 1
Fax: (+ 49 951) 297 299 3
Email: info@entwicklung-staerken.de
www.entwicklung-staerken.de