Key words: CAPD, Event Related Potentials, Laser, attention problems, respiratory chain, ATP, Wire and Fire, Learning disabilities, conduct disorder

Hypothesis for a future application of a Laser-device in patients with symptoms of a developmental auditory processing disorder

Part I: Methodological basics

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ABSTRACT

This article provides a conceptualisation of research studies which should evaluate whether changes of electrophysiological late event related potential pattern (latency, amplitudes) could be used to reflect clinical changes from therapeutic intervention with LASER light in patients with symptoms of central auditory processing disorder. The contingent negative variation (CNV) of event related potentials reflects a synchronization of together firing wired neural assemblies responsible for auditory processing, suggesting an accelerated neuromaturation process when applying a LASER device stimulation. It will be discussed whether a LASER stimulation might be useful for a clinical improvement of distraction symptoms caused by auditory processing deficits. A model is presented explaining these effects by inducing the respiratory chain of the mitochondria.

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, attentional deficits and general developmental delay [1]. An increasing number of children appear to have hearing impairment in spite of normal auditory thresholds. Parents and teachers describe difficulties in listening in the presence of background noises and difficulties in understanding rapid or degraded speech. In these cases, listening problems result from dysfunctions of auditory processing inside the brain and will be considered as central auditory processing disorder (CAPD) [3, 4, 5, 6]. 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 results suggest that neuroplasticity and neuromaturation are dependent on stimulation [1, 3, 7]. 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. Stages of neuromaturation are i) neurostimulation, ii) neuromodulation iii) neurorelaxation and iv) neurodifferentiation [7, 8]. This article refers mainly to the neurostimulation part: if a relevant circuit is turned on, it fires and the blood flows to this circuit. The brain scan (functional Magnetic Resonance Tomography (MRT)) is running like this. Neurostimulation is effective in preparing the brain to build new circuits (internal neuroplastic stimulation). Energy based stimulation (light, sound, electricity, vibration, movement, substance) may help to revitalize dormant circuits to achieve homeostasis from external and internal sources. The purpose of this article is to introduce a conceptualization of studies for auditory-perception improvements of children with symptoms of an auditory processing disorder when applying laser light. A model will be presented to explain possible results using electron modelling and proton exchange inside the respiratory chain.

(RE)-WIRING A BRAIN WITH LASER LIGHT

Already Francis Crick speculated the challenge to find a way to turn on certain neurons, while leaving others unaffected [9]. Light might be used to turn on specific clusters (classes) of neurons, thus wiring these neurons not by substance-based (chemical) signals rather than by physical signals. Energy from light use light sensitized molecules thus transforming light into energy [10, 11]. Thus, different wavelengths of the light spectrum may have different effects on the organism. Wilden et al. [12] 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 enhanced 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. These investigation are mainly based on patients with tinnitus and sudden hearing loss, while developmental hearing problems are not considered.

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 may result in morphological alterations within the visual parts of the brain [13, 14]. Strategies for management 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. 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.

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 [1, 15]. Increase in auditory stimulation may result in morphological alterations within the auditory parts of the brain [3]. The ability of the auditory cortex to reorganize continuously throughout life span reflects the ability to acquire new skills and behaviours. Long-term potentiation is related to increases in the synaptic activity and efficacy following strong and repeated stimulation of a sensory system. There have been reports of morphological and structural alterations within nerve cells including increase in size and postsynaptic density along with alterations in late event potentials [3, 4, 16].

Usually cells wire and fire together i.e. in rhythm. Neurons work usually in large groups of neuronal assemblies, communicating electrically through distributed networks throughout the brain [7, 8]. If the neurons are not synchronized, they cannot generate enough strong, sharp signals to stand out against the background noise of all the other neuronal signals inside the brain. Neurons do not necessarily fall silent, but they continue to fire at a slower rate. Therefore, these cells mess up the function of the "normal" cells. This occurs in epilepsy, Alzheimer disease, brain injuries and learning problems because cells are out of synchronization, even if the neurons are far away from the "sick" neurons. Light might be used to turn on specific clusters (classes) of neurons. Light frequencies carry energy and provide different types of information. In this context, it could be already shown that distinct frequencies from a low level laser stimulate mitochondrial respiratory chain complexes by turning on and off processes inside the cell [17]. Single cells without eyes have light sensitive molecules on their outer membranes that supply them with energy. Halobacterium for example reacts differently on wavelengths (frequencies) [18]. Energy from light use light sensitized molecules transforming light into energy. Thus, different wavelengths of the light spectrum have different effects on the organism. Szent-Györgyi [19, 20] discovered, that when an electron is transferred from one molecule to another within our bodies, the molecules can change their colour, i.e. they change the type of light they emit. Where does the energy come from and what are the energy analogues?

MODEL OF EXPLANATION USING ELECTRON MODELLING AND PROTON EXCHANGE INSIDE THE RESPIRATORY CHAIN.

The model of the cellular photobiological chain reaction caused by visible light to near-IR radiation of specific wavelengths (frequencies) reported by T.J. Karu [21-25] is used. Karu´s model is based on the analogy between the effects of photosynthesis and respiratory chain [26, 27]. While photosynthesis is an anabolic process producing glucose from light energy, H_2O and CO_2, the respiratory chain inside the mitochondria is a catabolic reaction from glucose gaining energy. Use of comparable redox equivalents in different compartments (NADP vs. NAD, FAD vs. FD) makes it attractive to support the "Karu idea".

While photosynthesis is transforming light energy by using chlorophyll as photoreceptor to gain the energy equivalent ATP, the respiratory chain does not really need light for running to gain the energy equivalent ATP. Both processes (photosynthesis, respiratory chain) are running the ATP synthesis by using high proton gradients to build up ATP from ADP and phosphate. This process is called "oxidative phosphorylation". Both processes are similar in terms of function of the ATP synthase. [27].

The respiratory chain process is running "substance-based" in healthy cells without light support. In the case of sick cells, it may be speculated that the energy production is reduced and can be recovered and supported by photooxidation process stimulation apart from substance substitution [26]. This means, there is a light induced transfer of an electron by a physical process instead of a chemical oxidation from a donating to an

accepting molecule, which will be reduced. Absorption of photons by light-absorbing molecules enhance electron transport chain function [17, 21, 28-30]. The energy from the absorbed photon will be transferred to redox centres of the respiratory chain, achieving an increase in ATP synthesis [21, 26]. The light induced increase of ATP synthesis and the construction of a photon gradient lead to an increased activity of the Na^+/K^+ and Ca^+/K^+ Antiporter and other ATP driven ion carriers like the NA^+/K^+ ATPase and the Calcium ATPase. ATP controls the cAMP level, both Ca^{2+} and cAMP stimulate DNA and RNA synthesis which leads to an increased cell repair mechanism [26].

It has been already demonstrated by Karu and others that the so called "antenna pigments", the flavoproteins and the cytochrome a/a3 of the cytochrome oxidase complex can be considered as sensitive light receptors on the cell membrane [22, 31, 32, 33]. Further investigations demonstrated that there is a variety of additional light absorbing molecules (chromophores) capable of absorbing photons at the membrane and mitochondria level [22, 34]. Altogether, specific wavelengths (multiwavelenght sources, NIR wavelength source, low power and high power laser etc.) may induce the respiratory chain of sick neurons thus leading to a modulation of mitochondrial regulation contributing to a molecular and cellular ATP driven repair mechanisms [17, 25, 35]. Monici et al. showed that laser treatment leads to a cytoskeletal rearrangement and expression of early differentiation markers [36] leading to an up-regulation and/or modulation at the protein level (cytoskeleton organization). Further on it may be speculated that epigenetically DNA synthesis can be increased by using distinct wavelengths of the light and NIR spectrum.

EVENT RELATED AUDITORY CORTICAL POTENTIALS (AERP)

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.

Recording of the Contingent negative variation (CNV) requires the patient to pay active attention to a stimulus. AERP´s are presumed to be related to attention, recognition, and memory processes. Event related cortical potentials allow the evaluation of brain activities. 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 is related to the synchronous firing of wired neurons in order to provide the ability of reaction capacity of a certain brain task.

Other studies emphasized the feasibility of using P300 event related potentials to document levels of auditory dysfunction [37, 38]. 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 [4, 16, 39]. Jirsa [40] 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. It seems reasonable to assume that changes in the morphology of the waveform correlates 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 must be confirmed by follow up investigation.

CONSEQUENCES

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 / unforming 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 [41]. Learning skills are encoded in the cumulative electrical patterns resulting from the neurons firing together [41, 42]. 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.

Because auditory neuromaturation and neural plasticity depend on distinctive stimulation of auditory neurons, dynamic management of CAPD should begin as early as possible. Studies 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. in the case of auditory processing (44). Studies on AERP measures performed before and after specific Laser light stimulation are in progress, to demonstrate possible therapeutic advantages of such a device and will be presented in Part II of this article. Furthermore, we need more information about the distinction of the different kinds of auditory processing disorders and clear cut-off definitions in the electrophysiological data. Our descriptions of performance disorders range from ADHD, visual and auditory processing disorders related to all-inclusive learning disabilities, minimal brain damage or minimal cerebral disorder in kindergarten and school age children. 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 [45]. Future research has to address these questions to enhance specificity 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 [46, 47]. Part II of this article will describe the experience with an infrared application in patients with auditory processing disorder evaluated by event related potentials using Multiwave looked system (MLS®) laser device (ASA S.r.l.) with wavelengths 808 and 905 nm.

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CONFLICTS OF INTEREST

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

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