Assessment of Cortical Inhibition in Adult Attention-Deficit/Hyperactivity Disorder by Paired-Chirp Auditory Evoked Potentials

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***Abstract*— In order to further research cortical impairment in ADHD patients, late auditory evoked potentials were measured. By using paired-chirp auditory late responses, we compared the ADHD group against a control group, focusing on the inhibition elicited by the stimuli. The results show overall smaller amplitudes in the N100 and P200 waves, as well as a reduced inhibition in test chirp for ADHD patients. A frequency study using the wavelet phase synchronization stability transform was made in order to strengthen the results, as well as analysis of variance test for frequency and reproducibility index for amplitude. Both amplitude and frequency show there is an impaired auditory inhibition for ADHD patients for 500 and 700 ms, and contribute to demonstrate that impairments in this condition are present in multiple cortical areas.**

I. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a frequent psychiatric disorder with cross-national prevalence for adults of 3.4% [1]. ADHD begins in childhood, continues in adolescence and remains verifiable in adulthood up to 60% as complete or partial symptomatic [2]. Psychopathology of ADHD is characterized by three dimensions: inattention, hyperactivity and impulsivity. ADHD comes along with deficits in cognitive as well as social ability and performance. Therefore ADHD denotes a considerable public health burden underlying the necessity to optimize diagnosis and therapy of ADHD across the lifespan.

Since diagnosis is partially subjective, it is important for the results in which it is based, to be as accurate and representative as possible, and not dependant on factors such as the mood of the person, his or her will to cooperate, or IQ, among others.

It has already been proven that there is indeed cortical impairment within ADHD patients. In [3] and [4] motor cortex excitability has been studied. Some of the observed impairments are not exclusive of ADHD pathologies [5]. Cortical excitability can also be studied by means of event-related potential (ERP), which can even help in diagnostic procedures [6]. There is sufficient literature that supports the ERP as an useful technique [7], [8], [9]. Among ERP, auditory evoked potential (AEP) can be coupled with a paired stimulation, in which the subject receives both a conditioning stimulus as well as a test stimulus; variations in intensity, frequency, stimulus used, as well as the interstimulus interval (ISI) elicit different results. By using a long term inhibition (500-1100 ms (ISI), [10]), identical-paired auditory stimulation, the cortical response to the second stimulus becomes smaller in terms of amplitude. The de Boer chirp, which produces simultaneous displacement along the cochlea by compensating frequency-dependent traveling-time differences, can be used for this purpose [11].

The focus of this study is to assess the feasibility of paired-chirp ALR as a way to test cortical excitability in adult ADHD, to compliment information on auditory processing when pathological conditions are present, and whether these conditions affect specific cortical regions or are localized and factor-dependant.

II. Method

A. Participants

The study was held at the Neurocenter, Saarland University Hospital, in Homburg, Saarland (Germany), performed on 30 right-handed subjects (16 male, 14 female), ages ranging from 20 to 47 (30.73 ± 9.02): 15 ADHD patients, recruited from a specialized ADHD ambulance clinic for associated disorders and 15 control subjects, with similar sex and age to ADHD group, recruited from the social environment of the authors. The current study was approved by the local ethics committee and was performed in accordance to the Declaration of Helsinki principles. Only participants who gave written informed consent after oral and written explanation about the aims of the investigation were enrolled. ADHD patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. Thereby self assessments (Wender-Utah Rating Scale (WURS-k) [12], [13]; ADHD self-rating scale (ADHD-SR, [14])) and semi-standardized diagnostic interviews (ADHD-DC [14]; WRI [15]) were used. Providing childhood ADHD symptoms according to a sum score of minimum 30 points in the WURS-k, ADHD patients fulfilled diagnostic criteria of DSM IV for adult ADHD, combined type, corresponding to ADHD-SR in self ratings. In addition criteria of the specialist ratings ADHD-DC and WRI for adult ADHD, combined type (DSM IV), were fulfilled. None of the subjects showed any further axis 1 diagnosis verified

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by SKID-II. A clean drug screening was precondition for participation in the study. Further exclusion criteria were any history of neurological events, such as brain injuries or any kind of vascular, inflammatory or degenerative brain disturbance. Clinical data from the self assessments (MWT-B, WURS-k, ADHD-SR) and semi-standardized diagnostic interviews (ADHD-DC) is shown in Table I. Prior and after the study, an audiogram was performed in order to verify that all the subjects had a normal hearing threshold level [16].

B. Stimuli

Two paired, identical chirps (frequency range: 100-10,000 Hz; intensity: 100 dB peSPL), a conditioning chirp (CC), followed by a test chirp (TC), were used. They were played through isolating headphones (HDA 200, Sennheiser GmbH, Germany) into the right ear of the subject, while the left headphone was muted. The delay between the chirps was chosen in order to elicit long term inhibition [10]. The ISIs chosen were 500, 700, 900 and 1100 ms, with 8 seconds between each pair of chirps, and a total of 40 pairs played for each ISI. Subjects were seating comfortably in a treatment chair, with their eyes closed; were asked not to sleep and move as little as possible. They were not required to focus on the chirps or any task-related activity.

C. Data acquisition

Small pellet, Ag/AgCl electrodes were placed in the right mastoid (ipsilateral to stimuli), left mastoid (contralateral), vertex (reference) and forehead (ground), to acquire EEG signal. The electrode impedances were kept at 5 KΩ or less. Data was acquired at 512 Hz sampling frequency, by means of an USB, 16 channel, 24-bit biosignal amplifier (g.USBamp, Guger Technologies, Austria). No online filtering was used, only post-filtering. The audio file for the chirp was a stereo-recorded file, containing in one channel the chirp sound and in the other a trigger signal, used as a time reference of the chirp for post processing. This trigger signal was converted from audio to a TTL signal via triggerbox (g.TRIGbox, Guger Technologies, Austria) and also acquired with the USB amplifier.

TABLE I
CLINICAL DATA FOR ADHD DIAGNOSIS (N=15)

	Group (M ± SD)		Statistic
	ADHD	Control	ANOVA
MWT-B (IQ)	103.7±14.2	108.7±13.8	F=0.981; p=0.330
WURS-k score	44.1±15.1	11.0±17.8	F=30.212; p=0.000
ADHD-SR:			
inattention	20.4±3.5	5.9±9.4	F=30.895; p=0.000
hyperactivity	19.3±4.4	3.9±7.8	F=44.891; p=0.000
total score	39.7±5.5	9.8±16.6	F=43.908; p=0.000
ADHD-DC:			
inattention	16.4±5.0	2.6±6.2	F=44.774; p=0.000
hyperactivity	16.9±5.4	1.5±2.4	F=101.337; p=0.000
total score	33.3±9.0	4.1±7.7	F=90.805; p=0.000

D. Data Processing

The output file consisted of two EEG channels, one trigger channel and a time vector. The settings of the amplifier, such as active channels, impedance check and output files were handled in SIMULINK (The Mathworks Inc, U.S.A.). The trigger signal was converted to 0 and 1 by means of a real-time relay. After the acquisition, both the EEG and the trigger signal were processed in MATLAB (The Mathworks Inc, U.S.A.). The first 50 EEG samples were removed via baseline correction, due to the USB amplifier having a slight delay which caused an artifact. Also, the mean of EEG was subtracted from the whole signal, as a way to remove offset. Filtering for EEG was made with a window-based FIR bandpass filter (2-30 Hz). Then, using the trigger signal as a reference, the EEG was segmented into one-second sweeps (512 samples), being 0 the moment when the trigger was identified. Once segmented, an artifact filter (50μV) was used to ensure that any sweep which presented higher amplitudes were discarded. The sweeps were then analyzed using Wavelet-Phase Synchronization Stability transform (WPSS). This transform is explained in depth in [17] and provides a time–scale (the scale is linked to a frequency range) representation of transient signals. Only measurements with at least half of the sweeps were taken into account. Both CC and TC sweeps for each run were paired (i.e. the same sweeps used between them and the same sweeps discarded in both when one of them presented artifacts). All the post-processed information was saved for further analysis.

E. Data Analysis

Once the data was processed and plotted, the analysis focused both on amplitude and phase. For amplitude study, the mean level of inhibition (amplitude difference between CP and TP in N100 and P200 waves) for all the ADHD patients was compared with the mean level of inhibition for all controls. Analogically, the phase study showing condition chirp against test chirp was evaluated. Validation methods for the data included reproducibility index (RI) kept over 0.55, as well as an analysis of variance (ANOVA) test for the mean of normalized WPSS difference in the 80-220 interval (CC and TC) between subjects and controls (considering p values under 0.05 significantly different).

III. RESULTS

A. Amplitude and phase analysis

Fig. 1 and 2 show the first 600 ms after-stimulus EEG measurement, both CC (normal line) and TC (dotted line), ipsilateral to stimuli. The mean for ADHD subjects and controls are plotted. Fig. 1 corresponds to the amplitude measurements and Fig. 2 corresponds to the WPSS transform. The WPSS were normalized for each subject before obtaining the mean.

B. Statistical analysis

The reproducibility index measurements for all ISI in EEG amplitude ipsilateral to stimuli are shown in Tables II(a)

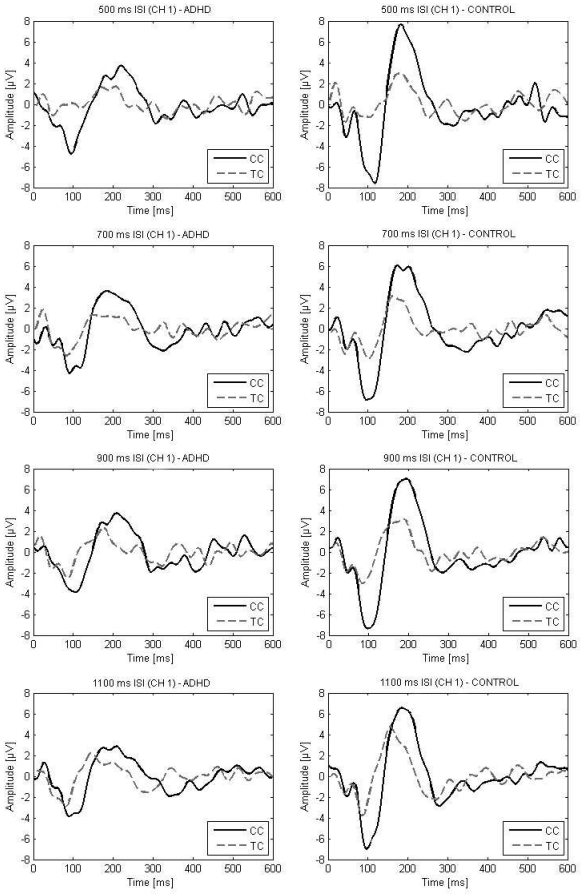

Fig. 1. EEG amplitude measurement for first 600 ms after stimulus (ipsilateral to stimuli, mean of all subjects). ADHD patients to the left, control group to the right.

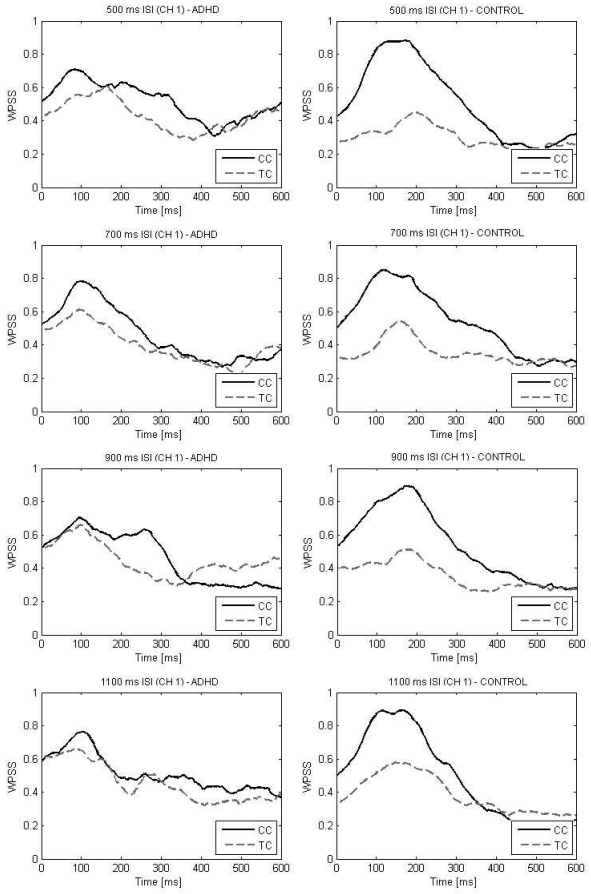

Fig. 2. WPSS transform for first 600 ms after stimulus (ipsilateral to stimuli, mean of all subjects, each subject was normalized previously). ADHD patients to the left, control group to the right.

(ADHD group) and II(b) (control group).
The ANOVA tests for WPSS are shown in Fig. 3, corresponding to the significant difference between mean inhibition for the 80-220 ms WPSS segment for patients and the same segment for controls, for all 4 ISI, ipsilateral to stimuli.

IV. Discussion

A. Amplitude analysis

As seen in Fig. 1, ADHD patients presented overall lower amplitudes for N100 and P200 waves, for all ISIs, suggesting a reduced cortical activation. The test chirp does not differ in amplitude to the condition chirp in ADHD subjects as much as in controls, however, for 900 and 1100 ms the inhibition was lower. The reproducibility indices for amplitude measurements report also generally bigger values for control group as shown in Table II, which indicates a more stable response from the control group to repeating stimuli.

B. Frequency analysis

The wavelet analysis shows a more dramatic difference between the ADHD and control groups. Fig. 2 shows almost no difference between CC and TC for ADHD patients, whereas the control group shows a clear difference for the 80-220 interval (containing both N100 and P200 waves). ANOVA tests for frequency analysis, focusing on the values

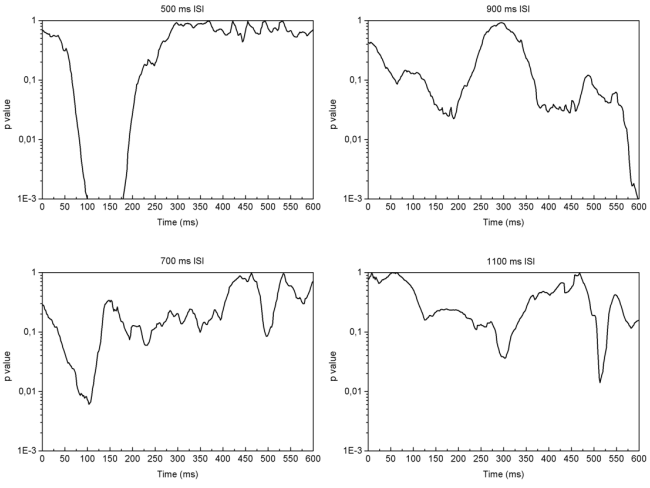

Fig. 3. ANOVA results for frequency analysis. The y axis (p value) is plotted in logarithmic scale. The range of interest is the 80-220 ms segment. As the ISI increases, the p value increases. Under 0.05 is considered significantly different.

TABLE II

REPRODUCIBILITY INDEX FOR AMPLITUDE MEASUREMENTS

(a) ADHD group

ISI	CC-N100	CC-P200	TC-N100	TC-P200
500	0.57 / 0.30	0.58 / 0.26	0.55 / 0.20	0.76 / 0.26
700	0.56 / 0.28	0.67 / 0.31	0.53 / 0.17	0.63 / 0.32
900	0.50 / 0.32	0.77 / 0.17	0.51 / 0.32	0.54 / 0.28
1100	0.53 / 0.30	0.56 / 0.29	0.63 / 0.26	0.62 / 0.30

(b) Control group

ISI	CC-N100	CC-P200	TC-N100	TC-P200
500	0.76 / 0.21	0.66 / 0.31	0.44 / 0.29	0.60 / 0.38
700	0.76 / 0.20	0.77 / 0.26	0.41 / 0.31	0.62 / 0.33
900	0.76 / 0.24	0.72 / 0.31	0.63 / 0.28	0.79 / 0.18
1100	0.75 / 0.19	0.57 / 0.34	0.67 / 0.26	0.61 / 0.26

in the 80-220 range show a significant difference for 500 and 700 ms ISI, staying under p=0.05, but not for 900 and 1100 ms. As discussed in [10], as ISI increases, the inhibitory effect achieved decreases.

V. CONCLUSIONS AND FUTURE WORK

A. Conclusions

In this study we assessed the feasibility of paired-chirp ALR as a way to test cortical excitability in adult ADHD. Results showed that this method may be used in order to study long-term cortical inhibition in such patients. Also the novelty was the use of a paired-pulse chirp. ALR may help gaining a better understanding from ADHD-related cortical impairment and its underlining symptomatic factors. Additionally, it may prove to be useful in the diagnostic process.

B. Future Work

Additional long-term inhibition paradigms for cortical inhibition are already in progress, in order to obtain more robust results and analyze how extensive can the cortical impairment be in the studied conditions.

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