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ORIGINAL PAPER

Assessment of post-excitatory long-interval cortical inhibition in adult attention-deficit/hyperactivity disorder

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Abstract In order to further examine cortical impairment in adult ADHD patients and to test the hypothesis of a disturbed neuronal inhibition in adults with ADHD, late auditory evoked potentials were measured. By using paired-chirp auditory late responses, we compared 15 adults with ADHD with 15 control subjects, focusing on the inhibition elicited by the stimuli. Besides amplitude measurements, a time–frequency phase coherence study using the wavelet phase synchronization stability (WPSS) was performed. ADHD was diagnosed according to DSM-IV criteria. All ADHD subjects were without medication and did not suffer from any further axis I disorder. WPSS analysis revealed impaired auditory inhibition for ADHD patients for interstimulus intervals (ISI) between 500 and 1,100 ms as compared with healthy controls. By analyzing the WPSS in the interval from 80 ms to 220 ms, mean inhibition of the test chirp was found to be 6% in the ADHD group and 38.5% in the control subjects ($p = 0.01$). Moreover, overall smaller amplitudes in the N100 and P200 waves at all ISI were found ($p = 0.04$ and $p = 0.02$). However, reproducibility indices in the amplitude measurements were low, thus supporting the use of the instantaneous phase-based analysis method. The results support the hypothesis of reduced intracortical inhibition as a correlate of disturbed brain function in adults with ADHD.

Keywords Adult ADHD · Neurophysiology · ERP · Inhibition · Wavelet phase synchronization stability

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a frequent psychiatric disorder that begins in childhood, continues into adolescence and remains verifiable in adulthood up to 60% as complete or partial symptomatic [1]. The transnational prevalence is 5.3% for childhood and adolescence [2] and 3.4% for adulthood [3]. Mainly three dimensions characterize psychopathology of ADHD: inattention, hyperactivity and impulsivity. ADHD comes along with deficits both in cognitive and in social ability and performance [4–6], and increases the risk of further psychiatric disorders [7]. Therefore, ADHD constitutes a considerable public health burden, with an obvious need to optimize diagnosis and therapy, especially in adults, since the condition was originally thought to be limited to children and adolescents [8, 53].

ADHD is a clinical diagnosis. Since it is insofar partially subjective, it is important for the results, on which it is based, to be as accurate and representative as possible, and not dependent on factors such as the mood of the person, his or her will to cooperate, IQ, among others. So far, there is an obvious lack of objective markers that can help confirm an ADHD diagnosis.

It has already been proven that there is indeed cortical and subcortical brain impairment in adult ADHD patients [9]. Structural and functional imaging studies, similar to those in children and adolescents, have suggested

dysfunction of frontal and parietal cortical regions in adults with ADHD [10–12]. At neuronal function level, motor cortex excitability has been extensively studied in adult ADHD patients and controls, using the technique of transcranial magnetic stimulation (TMS) [13–15]. In the studies of Richter et al. [13] and Schneider et al. [14], states of reduced intracortical inhibition were demonstrated, which resembled prior findings in children with ADHD [16]. However, some of the observed impairments are not exclusive of ADHD pathologies [17], indicating that impaired cortical inhibition is not specific to ADHD.

Cortical excitability can also be studied by means of event-related potentials (ERPs), which can even help in diagnostic procedures [18]. These potentials can be elicited using different modalities, for example, TMS, auditory, visual or somatosensory stimulation. There is sufficient literature that supports the ERP as a useful technique for the research of adult ADHD [19–23]. ERPs can be presented as a paired stimulation, in which the subject receives both a conditioning stimulus and a test stimulus. Variations in intensity, frequency, stimulus used, as well as the interstimulus interval (ISI) elicit different results. By using TMS, paired stimulation has already been established and studied as being able to both elicit short-interval cortical inhibition (SICI) (using 1–8 ms ISI) and facilitate (using 9–12 ms ISI) [51, 52]. Inhibition can also be achieved by means of a long, post-excitatory interval (LICI) [24, 48]. SICI is thought to be regulated by $GABA_A$ receptors [46, 47], whereas LICI has been shown to be mediated by $GABA_B$ receptors [42, 48].

LICI can also be elicited by means of auditory evoked potentials (AEP); since most of their early, middle and late components are between 0 and 1,000 ms, SICI presents some methodological problems. By using identical paired auditory stimuli at ISIs from 500 ms and higher, the cortical response to the second stimulus becomes smaller in terms of amplitude as a result of intracortical inhibition [49, 50]. The auditory stimuli used are usually tones or clicks. The de Boer chirp, which produces simultaneous displacement along the cochlea by compensating frequency-dependent traveling time differences [26], can be used as an appropriate auditory stimulus for this purpose. To the authors' knowledge, paired-chirp as an inhibitory paradigm has not been tested.

Although usually studied by means of amplitude and correlation coefficients, AEPs and in particular auditory late responses (ALRs), which focus on the evoked activity 50-ms post-stimulus (of specific interest for our project is the N1-P2 complex, in which the first negative trace is usually found within 80–120 ms post-stimulus and the positive trace within 180–220 ms; used as pointer in ADHD due to its role in sensory perception), can also be studied with phase stability measurements [27]. Since phase synchronization stability (PSS) of single-sweep ALR sequences has already been linked to attention [28, 29], it becomes a feasible option in order to study ADHD as well as more attention-impaired conditions.

The focus of this study was to assess the feasibility of paired-chirp ALR as a way to test cortical excitability in adult ADHD. We hypothesized that through PSS analysis, the features of paired-chirp ALRs can be used to discriminate between healthy subjects and ADHD patients in a more robust way than by using only an ALR amplitude/latency study.

Methods

Subjects

The study was held at the Neurocentre of the Saarland University Hospital (Germany), performed on 30 right-handed subjects (16 men, 14 women), with ages ranging from 20 to 47 years (mean age, 30.7 ± 9.02): 15 ADHD patients, recruited from a specialized ADHD ambulance, and 15 control subjects, with similar sex and age compared to the ADHD group, recruited from the social environment of the authors took part in the study. The current study was approved by the local ethics committee and was performed in accordance with 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 by a consultant psychiatrist specializing in adult ADHD, following in-depth clinical and psychological evaluations. In addition, standardized self-assessments regarding childhood (Wender-Utah Rating Scale; WURS-k) [30, 31] and current ADHD symptoms (ADHD self-rating scale; ADHD-SR) [32] were used. Semi-standardized diagnostic interviews according to the 18 DSM-IV criteria (ADHD-DC) and the Utah criteria for ADHD (WRAADDS) [33] have been performed in order to diagnose ADHD as accurate as possible [34]. Providing childhood ADHD symptoms according to a sum score of minimum 30 points in the WURS-k, criteria of the specialist ratings ADHD-DC and WRAADDS for adult ADHD, combined type (DSM-IV), were fulfilled in all ADHD patients. In addition, only those individuals who fulfilled diagnostic criteria of DSM-IV for adult ADHD, combined type, were included, corresponding to ADHD-SR in self-ratings.

None of the subjects showed any further axis 1 diagnosis verified by SCID-I. Patients and control subjects did not meet diagnostic criteria for any personality disorder

according to DSM-IV (axis II). Exclusion criteria also included any history of neurological events, such as brain injuries or any kind of vascular, inflammatory or degenerative brain disturbance, low intelligence (IQ $\leq$ 85) and taking any psychoactive medication. A clean drug screening was preconditioned for participation in the study. All participants were right handed, as determined by preferred writing hand. Prior to and after the study, an audiogram was performed in order to verify that all the subjects had a normal hearing threshold level [35]. Age, gender distribution and clinical data from the standardized assessments (MWTB, WURS-k, ADHD-SR, ADHD-DC) are shown in Table 1.

Stimuli

Two paired, identical chirps (frequency range: 0.1–10 kHz; intensity: 80 dB peak equivalent sound pressure level), 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 LICI [25]. The ISIs chosen were 500, 700, 900 and 1,100 ms, with 8 s 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; they 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. There were two examiners monitoring the subjects at all times; in case a patient opened the eyes or made abrupt movements, the experiment would be restarted.

Data acquisition

Four small pellet Ag/AgCl electrodes were placed in the right mastoid (ipsilateral to stimuli, identified as channel (1)), left mastoid (contralateral to stimuli, identified as channel (2)), vertex (reference) and forehead (ground) to acquire the EEG signal. The electrode impedances were kept at 5 KΩ or less. Data were acquired at 512 Hz sampling frequency, by means of a 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 the right channel the chirp sound and in the left channel (muted for the subject) 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 amplifier.

Data processing

The output file consisted of two EEG channels (right and left mastoid, i.e., ipsilateral and contralateral to stimulus), one trigger channel and a time series. The settings of the amplifier, such as active channels, impedance checks 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 digital data elements acquired, equivalent to the first 0.098 s of the complete measurement, were removed via baseline correction using the data 40 ms before the stimulation as reference, due to the USB amplifier having a slight delay, which caused an artifact. This artifact was present only at the beginning of the recording and had no influence on the recording of evoked potentials (the audio file starting seconds after the data acquisition); therefore, there was no need to correct it after the measurement started. The mean of the EEG was subtracted from the signal as well, as a way to remove offset. Filtering for the EEG was made with a window-based FIR band pass filter (2–30 Hz). Then, using

Table 1 Clinical data of ADHD and control subjects (Means, SD)

	ADHD ($N = 15$)	Controls ($N = 15$)	Statistics (ANOVA)
Male/female	9/6	8/7	
Age (years)	33.3 ± 10.5	28.0 ± 7.1	$F = 2.651$; $p = 0.115$
IQ	103.7 ± 14.2	108.7 ± 13.8	$F = 0.981$; $p = 0.330$
WURS-*k* total 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/impulsivity	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/impulsivity	16.9 ± 5.4	1.5 ± 2.4	$F = 101.337$; $p = 0.000$
Total score	33.3 ± 9.0	4.1 ± 7.7	$F = 90.805$; $p = 0.000$

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 (50 μV) was used to ensure that any sweep that presented larger amplitudes was discarded. Excessive movement, opening of the eyes or bad electrode contact at any stage of the measurement, could cause such artifacts. The subjects were supervised at the time of the recording, where the staff members took care of monitoring such events. The sweeps were then analyzed by wavelet phase synchronization stability measurement (WPSS), using the sixth derivative of the complex Gaussian as wavelet. This measure is based on the wavelet transform [36] and provides a time-scale (the scale is linked to a frequency range) representation of transient signals. The phase synchronization studies the instantaneous phase value for each sweep, in a specific moment of time. The sum of all phase values approaches 1 when they are synchronized (i.e., similar phase) and decreases as the phase value diverges. The values between 0 and 1 are then plotted in time and indicate the synchrony of the evoked potentials for relevant intervals (for example, 100 and 200 ms for N1 and P2, respectively). The details about the WPSS for single-sweep sequences of ALRs can be found in [27, 29]. Only measurements with at least half of the sweeps (20 out of 40 possible) were taken into account. The number of sweeps was chosen in order to have regularity in the acquisition and to be certain that the results were representative of the complete study; it would be often observed that the data from ADHD patients were not as regular as the data from controls; therefore, keeping at least half of the sweeps helped preserving only robust measurements (dropout criteria included subjects whose measurements had not enough sweeps after the artifact filtering). Both CC and TC sweeps for each run were paired (i.e., the same sweeps used for both and the same sweeps discarded when either CC or TC presented an artifact in that sweep). All the post-processed information was saved for further analysis. The overlap of the conditioning chirp with the test chirp did not interfere with the comparison, due to the ISI being out of our range of interest (80–220 ms).

Data analysis

Once the data were processed and plotted, the analysis focused on the time-scale phase coherence using the WPSS. The mean values of the normalized WPSS difference in the 80–220 intervals between CC and TC were compared, by means of analysis of variance (ANOVA) tests. P-values of 0.05 and below were regarded as significantly different. Moreover, N100 and P200 amplitudes after CC in ADHD subjects and controls were compared at ISI 500–1,000 ms by ANOVA. For validation of amplitude measurements reproducibility indices (Pearson's correlation between the averaged waveforms to even and odd numbered stimuli) were evaluated. The reproducibility index (RI) compares the linear relationship between signals; varies between −1 and 1, in which no relationship between both will return zero, while a perfect (or perfect inverse) match will return 1 (or −1). The sweeps were split into odd and even numbers for the RI analysis, and processed via MATLAB functions. Correlations between ADHD ratings and ALR results were also calculated according to Pearson.

Results

Wavelet phase analysis

WPSS transform data of the first 600 ms after ipsilateral CC (normal line) and TC stimulation (dotted line) is shown in Fig. 1. The WPSS data were normalized for each subject before obtaining the mean. There was almost no difference observed between CC and TC in the ADHD group, whereas the control group showed a clear difference for the 80–220 interval, which contains both N100 and P200 waves. The ANOVA tests for WPSS are shown in Fig. 2, 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 ISIs, ipsilateral to stimuli. As the ISI increases, the p-value increases. Significant differences were found for 500, 700 and 900 ms ISI ($p < 0.05$), but not for 1,100 ms.

Relative reduction in WPSS measurements was significantly higher in controls as compared to ADHD subjects at ISI 500, 700, 900 and 1,100 ms, respectively (Table 2). The mean ALR magnitude equivalences between CP and TP were 94% in the ADHD group and 61.5% in the control group (ANOVA, $F = 7.66$, $p = 0.02$). The level of the WPSS signal of the 80–220 ms interval after test chirp in relation to the WPSS signal after conditioning chirp ranged from 79.6 to 99.8% in the ADHD group and from 53.2 to 71.0% in the control group, suggesting reduced inhibitory activity in individuals suffering from ADHD. A greater percentage value accounts for reduced inhibition, that is, a value of 100% would mean that the amplitude of TC is the same as the amplitude of CC (no inhibition), while a value of 25% would mean that the amplitude of TC is only a fourth of the amplitude of CC (increased inhibition).

Amplitude, reproducibility index and correlations

Table 3a shows the N100 and P200 amplitudes after CC, ipsilateral to stimuli. ADHD patients presented overall significant lower amplitudes for N100 and P200 waves than

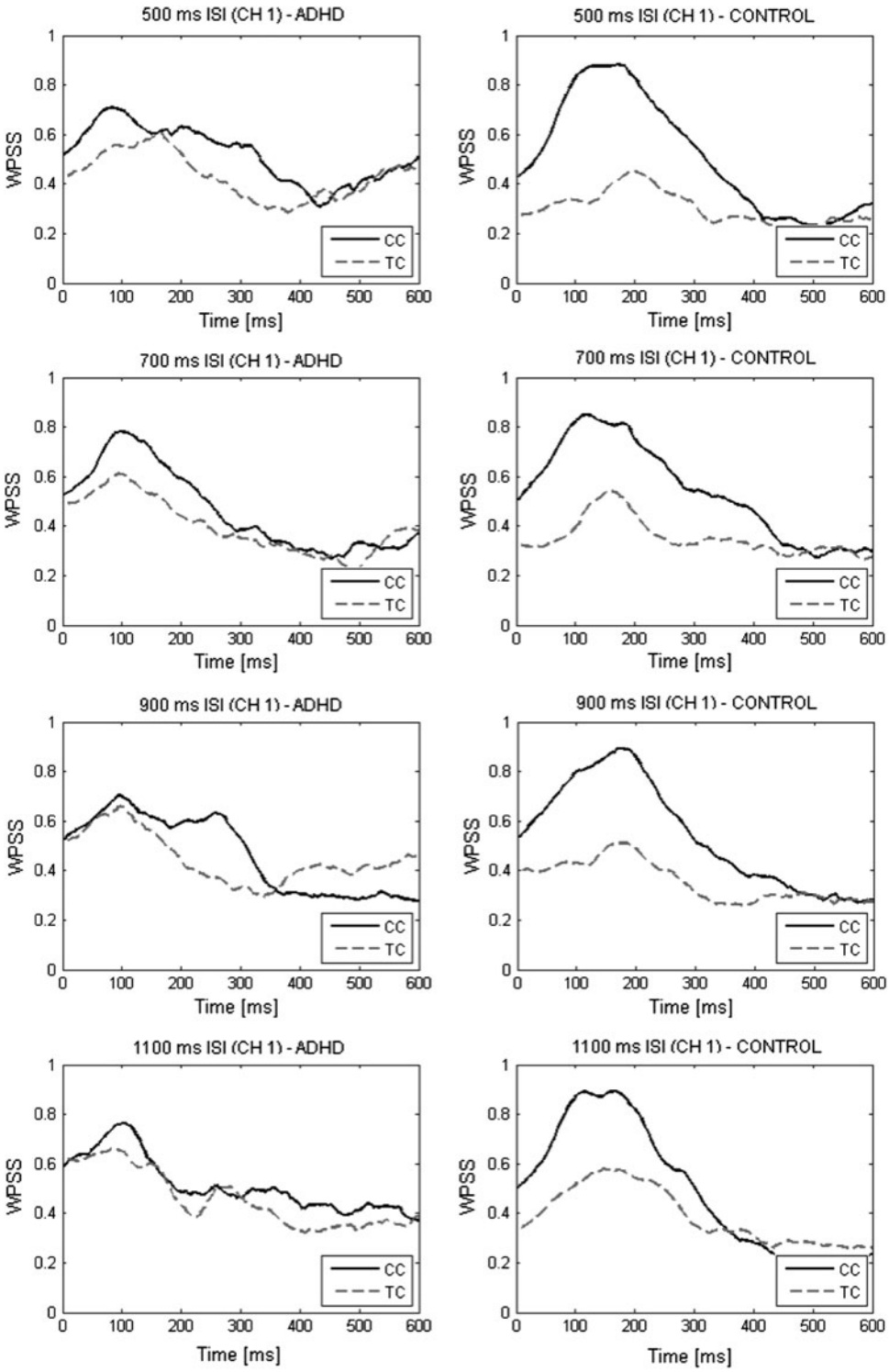

Fig. 1 WPSS transform for first 600 ms after stimulus (ipsilateral to stimuli, mean of all subjects; each subject was normalized previously) of ADHD patients and controls

control subjects, for all ISIs, as shown in Fig. 3. The mean N100 amplitude was -6.05 ± 0.57 μV in the ADHD group and -9.43 ± 0.52 μV in the control group (ANOVA, $F = 6.54$, $p = 0.04$), and the mean P200 amplitude was 5.73 ± 0.42 μV in the ADHD group and 8.76 ± 0.35 μV in the control group (ANOVA, $F = 5.80$, $p = 0.02$). Corresponding to these findings, at each ISI, the differences between the amplitudes after CC and TC were significantly lower in ADHD subjects as compared with controls (Table 3b). The absolute mean differences between CC and TC were 2.15 ± 0.64 μV in the ADHD group versus 5.24 ± 1.08 μV in the control group (ANOVA, $F = 11.06$,

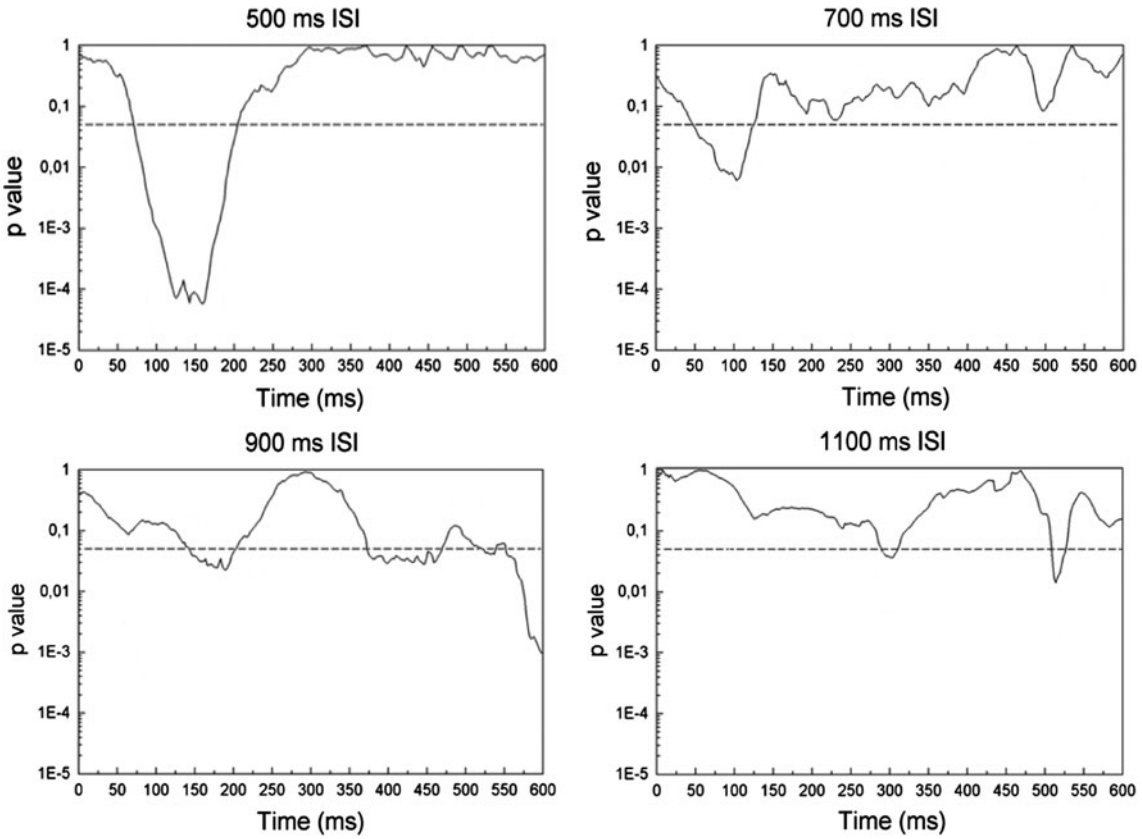

Fig. 2 ANOVA results for frequency analysis. The *y*-axis (*p*-value) is plotted in logarithmic scale. The range of interest is the 80–220 ms segment

Table 2 Wavelet phase synchronization stability in the 80–220 ms interval after test chirp in relation to the measurement after conditioning chirp

	WPSS inhibition (TC/CC) (%)		
ISI (ms)	ADHD ($N = 15$)	Controls ($N = 15$)	ANOVA (F/p)
500	98.82 ± 45.18	53.19 ± 15.49	13.69/0.00
700	79.63 ± 26.72	60.12 ± 16.56	5.78/0.02
900	99.80 ± 55.45	61.78 ± 24.26	5.92/0.02
1,100	97.77 ± 35.79	70.99 ± 27.82	5.23/0.03
Mean	94.00 ± 9.62	61.52 ± 7.33	7.66/0.02

Lower percentages indicate higher inhibition

$p = 0.03$) for N100 amplitudes, and 1.98 ± 0.70 μV in the ADHD group versus 3.93 ± 0.75 μV in the control group (ANOVA, $F = 4.60$, $p = 0.05$) for P200 amplitudes.

The reproducibility indices for amplitude measurements reported generally higher values for control group as shown for all ISIs. In particular, for N100 measurements, higher stability and lower variability were found in controls as compared to ADHD individuals. Reproducibility indices for N100 and P200 amplitudes ipsilateral to stimuli in the ADHD and the control group are shown in Table 4.

No significant correlations between the relation of the amplitudes after test and conditioning chirp and ADHD symptom ratings (ADHD-DC and ADHD-SR subscores and total scores) were found. The correlation coefficients are shown in Table 5.

Discussion

In this study, we assessed the feasibility of paired-chirp ALRs as a way to test cortical excitability in adult ADHD. Using wavelet phase stability analysis of the N100 and P200 waves, we demonstrated a significant reduction in intracortical inhibition of an auditory test chirp stimulus after a conditioning stimulus in adults with ADHD, as compared to controls. Thus, we found evidence for reduced inhibitory brain activity in adults with ADHD, as compared to healthy control subjects.

The N100 and P200 waves are commonly used for research of auditory attention [37, 38]. Due to a poor signal-to-noise ratio, amplitudes of these waves, however, are commonly evaluated by the average of a large number of sweeps in clinical settings. Therefore, it remains unclear whether a decrease in amplitudes of the average potential

Table 3 (a) N100 and P200 auditory evoked potentials amplitudes (μV) after conditioning chirp stimulation in adults with ADHD and controls (mean ± SD); (b) Differences between N100 and P200 auditory evoked potentials amplitudes (μV) after conditioning and test chirp stimulation in adults with ADHD and controls (mean ± SD)

	N100 (50–150 ms)			P200 (150–200 ms)		
ISI (ms)	ADHD ($N = 15$)	Controls ($N = 15$)	ANOVA (F/p)	ADHD ($N = 15$)	Controls ($N = 15$)	ANOVA (F/p)
(a) Amplitudes after conditioning chirp						
500	−6.16 ± 3.55	−9.91 ± 5.59	4.82/0.04	6.00 ± 3.55	9.11 ± 4.02	5.04/0.03
700	−6.22 ± 2.18	−9.04 ± 5.53	3.38/0.08	5.76 ± 2.20	8.37 ± 3.24	6.68/0.02
900	−6.58 ± 3.46	−9.84 ± 5.35	3.91/0.06	6.05 ± 2.68	8.99 ± 4.25	5.11/0.03
1,100	−5.24 ± 1.40	−8.93 ± 3.54	14.08/0.00	5.13 ± 1.68	8.56 ± 5.00	6.37/0.02
Mean	−6.05 ± 0.57	−9.43 ± 0.52	6.54/0.04	5.73 ± 0,42	8.76 ± 0.35	5.80/0.02
(b) Absolute amplitude differences (CC–TC)						
500	2.58 ± 1.55	6.80 ± 4.94	9.97/0.04	2.11 ± 2.30	4.87 ± 3.10	7.62/0.01
700	2.15 ± 2.34	4.82 ± 3.42	6.26/0.02	2.53 ± 2.16	4.03 ± 2.20	3.54/0.07
900	2.64 ± 3.29	5.04 ± 3.41	3.87/0.06	2.33 ± 2.38	3.79 ± 2.30	2.93/0.10
1,100	1.25 ± 1.24	4.29 ± 2.05	24.14/0.00	0.96 ± 1.42	3.04 ± 3.62	4.30/0.05
Mean	2.15 ± 0.64	5.24 ± 1.08	11.06/0.03	1.98 ± 0.70	3.93 ± 0.75	4.60/0.06

reflects a neuronal excitatory decrease or is the result of an instable phase. Also, habituation effects over the ongoing experiment cannot be ruled out when averaged data are used. One way to overcome these difficulties is the use of a time-scale measure, which is based on the phase information of single sweeps. This approach allows the evaluation of the quality and the stability of the response over the stimulus sequences in terms of the instantaneous phase information, which is independent from the fragile amplitude information. The WPSS thus represents a more robust measure of impaired cortical inhibition in adults with ADHD. A higher synchronization stability is expected within time ranges of evoked potentials. In healthy subjects, the synchronization clearly decreased for the test chirp, but ADHD subjects presented almost the same synchronization both for CC and TC conditions. This may suggest that, under normal conditions, the phase of ERPs is less synchronized in inhibitory processes.

Post-excitatory inhibition in response to paired stimuli has been usually considered to reflect presynaptic changes in transmitter release. There is considerable evidence that a system of gamma-aminobutyric acid (GABA) interneurons, which can be activated by both direct and indirect stimulations, may play a major role for inhibitory postsynaptic potentials [39]; but also dopaminergic transmission seems to be involved in the regulation of inhibitory processes in frontal cortex. It has been shown that spontaneous and evoked GABA release from cortical neurons is modulated by activation of dopaminergic D1-like receptors located on the presynaptic terminals of GABAergic neurons [40, 41]. From the two GABA receptors ($GABA_A$ and $GABA_B$), $GABA_B$ receptors are of special interest when studying LICI through paired-pulse stimulation, as shown by studies using transcranial magnetic stimulation, which proved that $GABA_B$ receptors are involved in controlling the magnitude of the inhibition at cortical level, by activating postsynaptic receptors, while presynaptic $GABA_B$ receptors reduce SICI [42]. Due to the latency of onset for $GABA_B$ inhibitory postsynaptic potential (20–50 ms) being longer than that of $GABA_A$ (3–5 ms), its influence in LICI can be inferred [43].

Despite the methodological problems of the amplitude-averaged responses, it is worth to refer to our findings of overall reduced N100 and P200 amplitudes after auditory chirp stimulation in adults with the clinical diagnosis of ADHD, which are consistent with findings in children with ADHD [44]. Thus, the results of this study indicate persistence of amplitude reduction in ADHD patients from childhood to adulthood. As already mentioned, there are problems regarding the correct interpretation of findings like this, which go along with averaged amplitude measures, as lower amplitudes in ADHD patients might indicate general interferences with background activity due to increased arousal in ADHD individuals, rather than to be a correlate of disturbed information processing. Also, the low reproducibility indices for N100 and P200 waves, particularly in the ADHD group, reflect the highly variable response to repeating stimuli in adults with ADHD and the more stable response from the control group. This encourages and supports the use of an analysis method that does not depend only on averaged amplitude measures, thus discarding the possibility of reduced amplitude being due to poor quality (i.e., low RI) measurements from ADHD subjects.

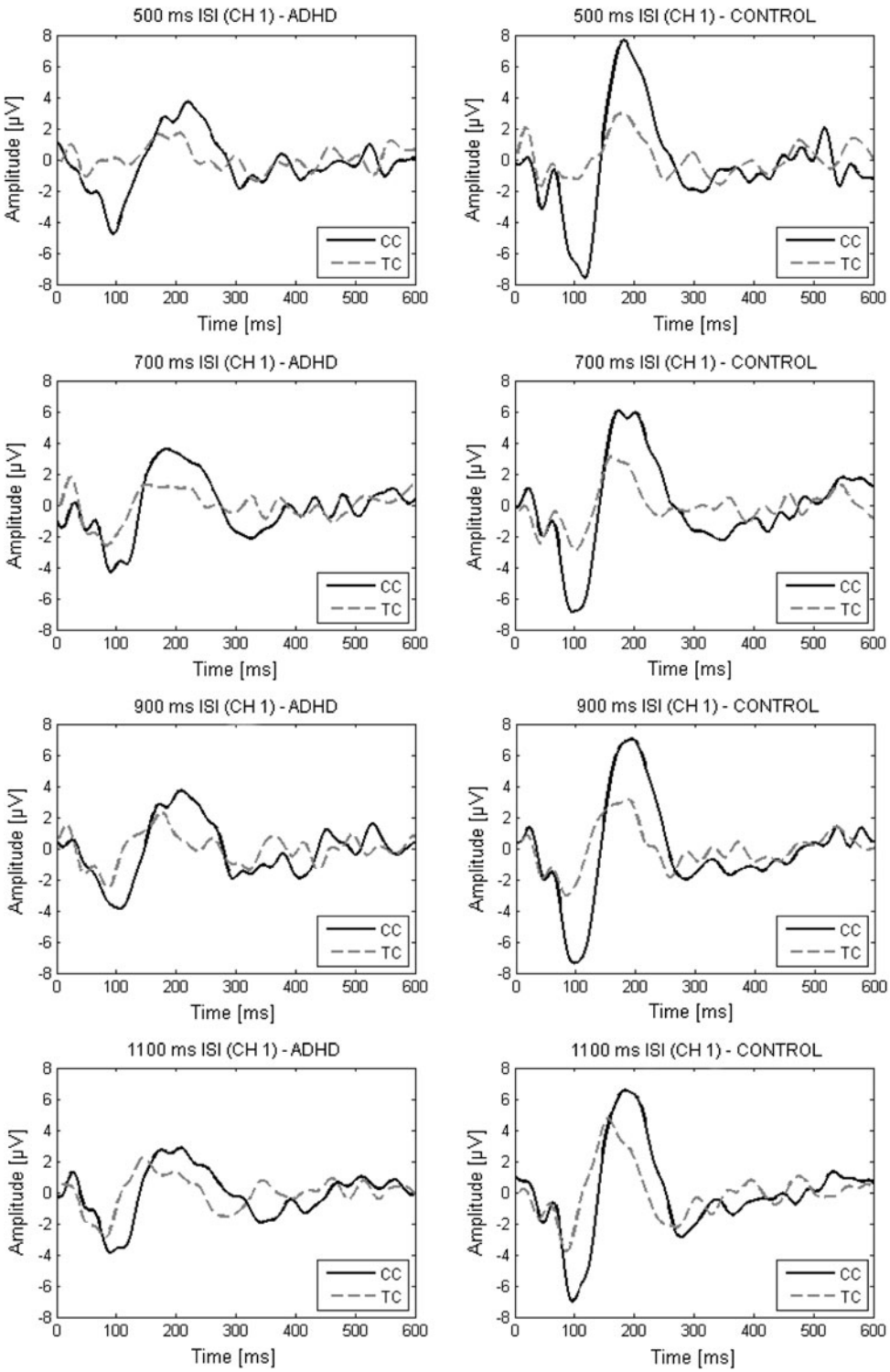

Fig. 3 Amplitude response for the first 600 ms after stimulus (ipsilateral to stimuli, mean of all subjects) of ADHD patients and controls

Our data did not show a correlation between the severity of ADHD psychopathology and the decrease in neuronal inhibition. Neither self- nor expert-rated scores of inattentiveness, hyperactivity/impulsivity, or both showed significant correlations with inhibitory deficits. At present, it cannot be ruled out that this might be a result from the small sample size, or from the low variability of clinical symptoms within the ADHD group. In addition, the existence of a threshold effect should also be considered.

Table 4 Reproducibility indices for N100 and P200 amplitude measurements of the ADHD and the control group after conditioning chirp

ISI (ms)	N100			P200		
	ADHD ($N = 15$)	Controls ($N = 15$)	ANOVA (F/p)	ADHD ($N = 15$)	Controls ($N = 15$)	ANOVA (F/p)
500	0.57 ± 0.30	0.76 ± 0.21	3.97/0.06	0.58 ± 0.26	0.66 ± 0.31	0.60/0.44
700	0.56 ± 0.28	0.76 ± 0.20	4.72/0.04	0.67 ± 0.31	0.77 ± 0.26	0.96/0.34
900	0.50 ± 0.32	0.76 ± 0.24	6.39/0.02	0.77 ± 0.17	0.72 ± 0.31	0.28/0.60
1,100	0.53 ± 0.30	0.75 ± 0.19	5.91/0.02	0.56 ± 0.29	0.57 ± 0.35	0.01/0.91

Table 5 Spearman's rank correlation coefficients (ρ) and statistical significance between ADHD ratings and AEP measurements at different ISIs

ISI (ms)	ADHD-SR			ADHD-DC		
	Subscore inattention	Subscore hyper/imp	Total score	Subscore inattention	Subscore hyper/imp	Total score
500	−00.081	−0.143	−0.164	−0.412	−0.253	−0.370
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
700	−0.021	0.371	0.121	0.252	0.362	0.239
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
900	0.247	0.358	0.543	0.107	0.313	0.136
	$p > 0.05$	$p > 0.05$	$p < 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$
1,100	0.238	−0.152	0.120	−0.011	−0.308	−0.239
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p > 0.05$

Similar findings of reduced neural inhibition tested with paired-pulse paradigms have also been reported for some other neuropsychiatric disorders like Parkinson's disease [25], Huntington's disease [45] and Schizophrenia [17]. Thus, the data presented here seem to be not specific for ADHD, but instead might represent a functional endophenotype related to disturbed attention control or ability to filter out repeated irrelevant sensory information. This has yet to be clarified and is an objective in future studies.

As the main goal of this study was to test the feasibility of LICI in ADHD, the results show that the method might be useful for the assessment of inhibitory impairment in such patients. ALRs may help gaining a better understanding from ADHD-related cortical impairment and its underlining symptomatic factors, as well as support current diagnostic protocols. Additional LICI paradigms for impaired cortical inhibition are already in progress, in order to obtain more robust results and to increase the specificity for different neuropsychiatric disorders.

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Conflict of interest The authors declare that they have no conflict of interest.

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