The role of comorbid depressive symptoms on long-range temporal correlations in resting EEG in adults with ADHD

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Abstract
Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder, characterized by core symptoms of inattention, hyperactivity and impulsivity. Comorbid depression is commonly observed in ADHD-patients. Psychostimulants are recommended as first-line treatment for ADHD. Aberrant long-range temporal correlations (LRTCs) of neuronal activities in resting-state are known to be associated with disorganized thinking and concentrating difficulties (typical in ADHD) and with maladaptive thinking (typical in depression). It has yet to be examined whether (1) LRTC occur in ADHD-patients, and if so, (2) whether LRTC might be a competent biomarker in ADHD comorbid with current depression and (3) how depression affects psychostimulant therapy of ADHD symptoms. The present study registered and compared LRTCs in different EEG frequency bands in 85 adults with ADHD between groups with (n = 28) and without (n = 57) additional depressive symptoms at baseline. Treatment-related changes in ADHD, depressive symptoms and LRTC were investigated in the whole population and within each group. Our results revealed significant LRTCs existed in all investigated frequency bands. There were, however, no significant LRTC-differences between ADHD-patients with and without depressive symptoms at baseline and no LRTC-changes following treatment. However, depressed ADHD patients did seem to benefit more from the therapy with psychostimulant based on self-report.

Keywords Long-range temporal correlation · LRTC · ADHD · Depression · EEG · Resting state

Introduction
Adult attention deficit/hyperactivity disorder (aADHD) is a frequent neurodevelopmental disorder with a worldwide prevalence of at least 2.8% [1]. It is characterized by dysfunctions in attention, behavior and emotion, in other words inattention (IA), hyperactivity (HY) and impulsivity (IMP) [2]. ADHD has a childhood onset and in about 60% of pediatric patients the symptoms persist into adulthood [3]. Comorbid psychiatric disorders are very commonly observed in aADHD [4] and can impact its persistence into adulthood [2].

In a range of studies, aADHD has been associated with co-occurrence of depressive disorder [5–7]. In self-evaluating assessments, depressed aADHD patients, when compared to patients had only ADHD, report a higher demand for previous mental health care [8], experience lower occupational functioning [9, 10] and perceive consequently lower quality of life [11]. Comorbid depression therefore presents important clinical challenges [12, 13] since its co-occurrence leads to greater illness burden and complexity than those individuals with aADHD or depression alone [11]. On the other hand, there is growing evidence from neuropsychological and electrophysiological studies that suggests no significant difference in cognitive performance [14] or in absolute power in specific frequency band measuring by electroencephalography (EEG) between depressed and non-depressed aADHD [15–18]. These results may question the usefulness and reliability of objective markers in differentiating between ADHD and depressive symptoms in adults. Several studies have
furtherly concluded that EEG cannot be recommended as an appropriate diagnostic tool for ADHD based on the current level of knowledge [19], but still has a potentially promising future [20]. To sum up, despite those result discrepancies requiring clarifications, considering the greater burden and complexity of comorbid ADHD and depression, other suitable objective, diagnostic EEG-based markers are needed.

Neural oscillations arising from synchronized electrical activity of numerous neurons during resting state are not random but follow complex temporal structures [21]. It was well demonstrated that these neural oscillations are correlated over thousands of oscillation cycles [22–24]. This is a phenomenon called long-range temporal correlation (LRTC) and has been observed in several EEG studies [21, 22, 24]. In heathy individuals, the LRTC reflects the adaptability, i.e. the ability to maintain the balance between stability and flexibility of neuronal assemblies [25]. The utilization of LRTC during resting state as an indicator for adaptability of neural system involving behavior [24], sensory [26] and cognition [27–29] became recently evident. Aberrant LRTC has been observed in several psychiatric or neurological pathological conditions: LRTC was stronger in seizure-affected areas in epileptic [30] and depressive patients [31, 32]. While LRTC was weakened in early-stage of Alzheimer’s disease [33] and in patients with schizophrenia [34].

ADHD is associated with several neurocognitive deficits including difficulty in inhibiting non-beneficial behaviors, poor working-memory, concentration abilities and emotional instability. ADHD shares symptoms liking cognitive impairments with Schizophrenia [34], depression [31, 32] and Parkinson’s disease [35]. Given the evidence utilization of LRTC in mentioned disorders as well as its sensitivity to brain maturation in humans, it has been suggested as a potential biomarker of pathophysiology in neurodevelopmental disorders, in particular ADHD [36]. However, to the best of our knowledge, LRTC has not yet been investigated in ADHD.

For the treatment of aADHD, psychostimulants are recommended as first-line treatment as they have been shown to improve attention and enhance central nervous system (CNS) arousal [37]. Given the accumulating evidence supporting the availability of LRTC in treatment evaluation in a range of neurodevelopmental and mental disorders [32, 38, 39], it is important to investigate whether LRTC are modulated by means of treatment with psychostimulants in patients with aADHD.

Furthermore, several previous studies demonstrated significant associations between LRTC and severity of depressive symptoms in clinically depressed patients [40–43] and aberrations in LRTC of depressed patients compared to healthy controls A recent study also showed that the normalization of LRTC is associated with depressive symptoms relief [32].

Against this background, the main aims of this study were to examine the presence of LRTC in aADHD in resting EEG and to investigate whether LRTC are modulated by means of pharmacological intervention with methylphenidate in these patients. The second aim of this study was to explore whether LRTC is yet a competent biomarker of pathophysiology in aADHD with additional depressive symptoms, and if so, how and to which extent the effect of pharmacological intervention with extended release methylphenidate is modulated by comorbid depressive symptoms.

Methods

Participants

Data of the current study were taken from a previously published multicenter, single-arm, open label clinical trial in ADHD patients [44] with a recruitment period from April 2016 to June 2018. This study was reviewed and approved by the local ethics committee (Registration: EudrACT 2015–000,488–15; German Clinical Trial Register DRKS00009971, University of Leipzig ethics committee 337/15-f). The methods utilized for patient inclusion and exclusion criteria have been described in detail elsewhere [44].

For the current analyses, patient data were included if they met the following criteria: clinical DSM-IV diagnosis of ADHD confirmed by a psychiatrist and psychologist, no evidence of current suicidality, anxiety or adjustment disorders, no history of substance abuse or dependence and no psychotic disorders. Patients also had to have completed a titration phase with extended release methylphenidate for 4 weeks. Exclusion criteria were demonstration of acute episodes of major depression according to ICD-10 during patient screening, pathological activity or excessive artifacts in resting EEG and remaining insufficient EEG epochs for LRTC analysis (see section EEG data analyses) at baseline or at the final visit, respectively.

Study design and measurements

ADHD symptom severity: At baseline, a set of self-report measurements was used to evaluate ADHD-related symptoms: the short German Wender Utah Rating Scale (WURS-k) [45] was administered allowing a retrospective diagnosis of ADHD in childhood. WURS-k manifests excellent retest-reliability (r = 0.90) and internal consistency (r = 0.91), significant correlations were found to impulsivity in Eysenck’s Impulsivity Questionnaire, and excitability, aggression, emotional instability and satisfaction on the Freiburg Personality Inventory in ADHD patients [45]. The German version of the Conners’ Adult
ADHD Rating Scale (CAARS) [46] was performed for a comprehensive assessment through three subscales consisting of DSM-IV ADHD symptoms (i.e. subscale DSM-IA, DSM-HY1 and DSM-G) and four empirically derived subscales consisting of inattention/memory problem (IA/ME), emotional lability (IMP/EL), hyperactivity/restlessness (HY/RE), and problems with self-concept (SC). Internal consistency of these four subscales ranged between 0.87 and 0.88, furthermore they have proved to show very good fit confirmatory factor analysis with model for American original [47]. In addition, CAARS contains a scale of ADHD-Index. This index includes nine items that best distinguish between adults with ADHD and healthy controls. Sum score of WUSR-k as well as age- and sex-corrected T-scores for each subscale of the CAARS were further included into the analysis.

Depressive symptom severity and group distinction: Severity of depression was assessed using the German Beck Depression Inventory-II (BDI-II) [48]. Its sum score was included in further analysis. Group distinction between ADHD patients with and without additional depressive symptoms was based on the cut-off score in the BDI-II: Patients with a sum score over 13 at baseline indexed existence of at least a mild depression and the depression was based on the cut-off score in the BDI-II: Patients with a sum score over 13 at baseline indexed existence of at least a mild depression and were thus allocated into the ADHD + group; the remaining patients with sum scores in range of 1 to 13 were allocated into the ADHD- group. Sum score of Montgomery–Asberg Depression Rating Scale (MADRS) [49] were collected as an external assessment of the degree of depression.

Clinical related symptoms. Moreover, a set of questionnaires was employed to assess other psychological problems and status of each participant: the Severity Scale of the Clinical Global Impression (CGI-S) is a 7-point scale that requires clinician to rate the overall clinical severity of a participants’ illness at the time of assessment. The German Inventory of Interpersonal Problems (IIP) [50] identified participants’ most salient interpersonal difficulties. Subjectively perceived quality of life in different domains was measured with the short German Version of the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF) [51].

Treatment. After diagnosis, all participants received 20 mg of extended release methylphenidate as initial dose. The dose was then increased weekly in steps of 20 mg until individual weight-based target doses (i.e. 40 mg/60 mg/80 mg per day) were reached. The dose could be adjusted or stopped due to any side effects at any time.

Reassessment. At the final visit, reassessment of all the above-mentioned instruments, except the WURS-k, allowed evaluation of the change from baseline due to the pharmacological intervention.

EEG recording

To collect EEGs in eyes-closed resting condition, all participants were placed in a semi-supine position in a sound-attenuated and temperature-controlled room. They were instructed to rest with their eyes closed for a 15 min recording session. EEG was recorded from 31 Ag/AgCl active electrode positions according to the extended international 10–20 system using EasyCap (Brain Products GmbH, Gilching, Germany). Each EEG channel was referenced to a common average. Two bipolar electrodes monitored horizontal and vertical eye movements. Electrode impedance was kept below 10 kΩ.

EEG data analyses

The EEG signal was analyzed in the Brain Vision Analyzer Software Version 2.1 (Brain Products GmbH, Gilching, Germany) and MATLAB (Version 2020a, The MathWorks, Inc., Natick, MA, USA). The data were first high pass-filtered at 1 Hz and down-sampled to 200 Hz. The first 10 min of the total 15 min EEG period were then selected in order to reduce the impact of different CNS arousal states on the LRTC in case participants had been falling asleep. Eye movements, muscle and cardiogenic artefacts were removed with an independent component analysis (ICA). After the ICA, the segmented EEG was recombined into continuous signals for subsequent analysis.

Afterwards, bandpass filtering was applied to filter signals in delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz) and beta (13–25 Hz) bands for all electrodes (an example signal of theta band at Fz site is illustrated in Fig. 1A). The Hilbert transformation was then applied to extract the amplitude envelope (red line in Fig. 1B) of the signals. The temporal structure of these amplitude envelopes was then analyzed using Detrended Fluctuation Analysis (DFA) [52] as implemented in a custom MATLAB script [32, 34]. DFA estimated the scaling of the root mean-square fluctuation of the intergraded and linearly detrended signal across different time windows [27], for the current study with a window size in range of 5–50 s. There was a nested artefact rejection function in DFA, with this the particular EEG segment exceeding an amplitude threshold ± 150 µV was marked as bad and ignored for further LRTC calculation. This step led to the exclusion of several participants for excessively bad EEG segments. The slopes of the least-squares lines were the scaling exponent (Fig. 1C) in a range of 0.5–1, where scaling exponent of 0.5 indicating for uncorrelated signals (e.g. white noise).
Statistical analyses

In order to minimize the number of comparisons and correlational analyses, we calculated the mean scaling exponent through averaging scaling exponents at each electrode site in the corresponding frequency band (i.e. mean LRTC). In case of significant results, we conducted exploratory post hoc analyses for each single electrode. Statistical analyses were conducted using SPSS Statistics 25.0 (IBM corp.; Armonk, New York).

The relationship between LRTC and clinical symptoms was quantified by calculating Person product-moment correlation coefficient between LRTC in corresponding frequency band, depressive and ADHD symptoms.

Before we performed statistical comparisons, we executed Kolmogorov–Smirnov Tests to examine the normality of distribution of relevant variables. The results of Kolmogorov–Smirnov Tests are summarized in supplementary file. According to these results, non-parametric tests were applicable for age, CGI-S, BDI, MADRS, CAARS, WURS-K and LRTC, while parametric tests were for QoL and IIP. Person Chi-Square Test were used for nominal variables (sex and dosage). The treatment related changes were investigated by paired-sample t-Tests/Wilcoxon Tests. Statistical significance value for these tests was set at 0.05.

Additionally, depending on the selected tests their corresponding between-group (ADHD + vs. ADHD-) and within-group (baseline vs. final) effect sizes (Cohen’s d or |r|) were calculated.

Results

Sample characteristics

The final sample consisted of 85 aADHD patients, who completed a titration phase with extended release methylphenidate for 4 weeks. There were 28 aADHD patients with additional depressive symptoms allocated into ADHD + group, while 57 aADHD patients without depressive symptoms in ADHD- group. This group distinction was based on the cut-off score (cut-off 13) in the BDI-II at baseline. Their main clinical characteristics are presented in Table 1.

Both groups are similar in sex, age and dosage. We obtained higher scores for individuals in the ADHD + group regarding depressive symptoms (MADRS) and clinical global impression (CGI-S) based on external assessment,
|                     | Baseline                                  | Final visit                               |
|---------------------|-------------------------------------------|-------------------------------------------|
|                     | ADHD+ (n=28) vs ADHD- (n=57)              | ADHD+ (n=24) vs. ADHS+ at baseline (p; effect size) vs. ADHD- (n=47) vs. ADHD- at baseline (p; effect size) vs. All (n=71) vs. all at baseline (p; effect size) |
| Females\(^a\)       | 10 (35.7%) vs 17 (29.8%)                 | 4.67 ± 0.86 vs 4.67 ± 0.86               |
| Age (years)\(^b\)   | 32.07 ± 7.40 vs 33.81 ± 10.12             | 6.48 ± 0.33 vs 6.48 ± 0.33               |
| Dosage\(^a\)        | 40 mg 2 (7.1%) vs 2 (3.5%)                | 6.06 ± 0.19 vs 6.06 ± 0.19               |
|                     | 60 mg 9 (32.1%) vs 15 (26.3%)             | 24 (28.2%) vs 24 (28.2%)                |
|                     | 80 mg 17 (60.7%) vs 40 (70.2%)            | 57 (67.1%) vs 57 (67.1%)                |
| CGI-S\(^b\)         | 5.04 ± 0.33 vs 4.48 ± 0.99                | 0.01; 0.353 vs 0.01; 0.353               |
| BDI\(^b\)           | 23.54 ± 8.03 vs 4.89 ± 3.94               | 7.5E-14; 0.811 vs 7.5E-14; 0.811         |
| MADRS\(^b\)         | 11.14 ± 3.26 vs 7.04 ± 3.49               | 4.0E-6; 0.504 vs 4.0E-6; 0.504           |
| CAARS\(^b\)         | DSM-G 80.86 ± 10.15 vs 78.38 ± 9.44       | 79.20 ± 9.6 vs 79.20 ± 9.6               |
|                     | DSM-IA 81.61 ± 10.74 vs 81.98 ± 8.34      | 81.86 ± 9.15 vs 81.86 ± 9.15             |
|                     | DSM-HYI 74.46 ± 13.35 vs 68.55 ± 11.82    | 70.52 ± 12.59 vs 70.52 ± 12.59           |
|                     | IA/ME 79.96 ± 10.49 vs 79.73 ± 9.63       | 79.81 ± 9.86 vs 79.81 ± 9.86             |
|                     | HY/RE 73.14 ± 12.09 vs 70.25 ± 13.56      | 71.21 ± 13.08 vs 71.21 ± 13.08           |
|                     | IMP/EL 73.86 ± 14.57 vs 63.64 ± 13.29     | 67.05 ± 14.48 vs 67.05 ± 14.48           |
|                     | SC 71.96 ± 11.08 vs 64.13 ± 14.42         | 66.74 ± 13.84 vs 66.71 ± 10.27           |
|                     | ADHS-Index 80.54 ± 8.92 vs 75.77 ± 8.56   | 77.36 ± 8.92 vs 77.36 ± 8.92             |
|                     | WURS-K\(^b\) 48.36 ± 11.46 vs 41.13 ± 11.41 | 43.57 ± 11.86 vs 43.57 ± 11.86         |
|                     | QoL\(^d\) 205.12 ± 43.10 vs 258.75 ± 39.20 | 1.52E-7; -1.324 vs 1.52E-7; -1.324        |
Entries are mean ± standard deviation or numbers (%)

Bold fonts indicate statistical significance; statistical significance value for these tests was set at 0.05

a Pearson Chi-Square Test for nominal variables, their effect sizes were estimate by Phi/Cramer’s V

b Mann–Whitney-Test for non-normally distributed variables, their effect sizes were estimate by |r|

c as a retrospective diagnosis of ADHD in childhood was only used at baseline

d Independent sample t-Tests for normally distributed variables, their effect sizes were estimate by Cohen’s d

e treatment related changes measuring by Wilcoxon Tests (effect size r), with exception of QoL und IIP. Their changes were measured by paired sample t-Tests (effect sizes Cohen’s d)

### Table 1 (continued)

|                      | Baseline | Final visit |
|----------------------|----------|-------------|
|                      | ADHD + (n = 28) vs ADHD- (n = 57) | ADHD + (n = 24) vs. ADHS + at baseline (p; effect size) | ADHD- (n = 47) vs. ADHD- at baseline (p; effect size) | All (n = 71) vs. all at baseline (p; effect size) |
| IIPd                 | 119.54 ± 26.05 vs 87.67 ± 32.74 | 99.35 ± 35.27 | 75.81 ± 30.73 | 83.54 ± 33.91 |
|                      | 2.2E-5; 1.037 | 0.004; 0.630 | 0.007; 0.392 | 8.60E-5; 0.442 |

CGI-S: Severity Scale of the Clinical Global Impression

BDI: Beck Depression Inventory

MADRS: Montgomery–Asberg Depression Rating Scale

CAARS: Conners’ Adult ADHD Rating Scale

DSM-G: DSM-IV and DSM-HYI: three subscales of CAARS consisting DSM-IV ADHD symptoms

IA/ME: Inattention/memory

HY/RE: Hyperactivity/restlessness

IMP/EL: Impulsivity/ emotional lability

SC: Self-concept

WURS-K: German Wender Utah Rating Scale

QoL: Quality of life as measured by German Version of the World Health Organization Quality of Life Questionnaire

IIP: Interpersonal problems as measured by German Inventory of Interpersonal Problems
than for those patients in the ADHD- group. The former also had significantly higher T-scores regarding currently ADHD severity as assessed by subjective rating (CAARS) and higher scores regarding ADHD severity in childhood based on subjective retrospective diagnosis (WURS-K). Furthermore, individuals in the ADHD + group as compared to those in the ADHD- group experienced more interpersonal difficulties (IIP) and lower quality of life (WHOQOL-BREF).

**LRTC in aADHD**

Since the scaling exponent provided a quantitative measure for the LRTC of EEG signals, the scaling exponent in the 0.5–1.0 range indicates the presence of LRTC. According to this criterion, the mean LRTC was significantly present in the delta (mean = 0.61 ± 0.05, range: 0.54–0.81), theta (mean = 0.64 ± 0.08, range: 0.53–0.82), alpha (mean = 0.72 ± 0.08, range: 0.54–0.92) and beta (mean = 0.71 ± 0.08, range: 0.55–0.93) bands. The topographical distributions (Figure S1) and descriptive statistics at each electrode site (Table S2) are summarized in supplementary file.

**Mean LRTC in resting EEG are uncorrelated with ADHD and depressive symptoms**

Table 2 shows detailed results for correlation analyses between mean LRTC and ADHD and depressive symptoms. There was a negative correlation between mean theta-LRTC and severity of depressive symptoms as measured by BDI scores ($r = -0.228, p = 0.036$) as well as between mean alpha-LRTC and T-score for subscale HY/RE of the CAARS ($r = -0.243, p = 0.026$), but they were not significant after Bonferroni correction ($p \leq 0.0125$). No further significant associations were found between mean LRTC measured at resting EEG and T-scores obtained via CAARS and BDI scores (Table 2).

**No difference in mean LRTC at baseline between ADHD + and ADHD**

Results of Mann–Whitney-U-Tests did not show any significant differences between ADHD+ and ADHD- regarding mean LRTC in the delta ($p = 0.695, |r| = 0.043$), theta ($p = 0.079, |r| = 0.191$), alpha ($p = 0.896, |r| = 0.097$) or beta ($p = 0.881, |r| = 0.016$) bands. It is of note that a small effect size ($|r| = 0.191$) was found for the difference in mean theta-LRTC between ADHD+ and ADHD-. Table 3 summarizes all related statistical results. The topographical distribution and comparisons between the groups at each electrode site are illustrated in Fig. 2.

### Table 2  Statistical results of correlation analyses between mean-LRTC and ADHD and depressive symptoms

| Assessment and subscales | Mean delta-LRTC | Mean theta-LRTC | Mean alpha-LRTC | Mean beta-LRTC |
|--------------------------|-----------------|-----------------|-----------------|----------------|
|                          | $r$  | $p$  | $r$  | $p$  | $r$  | $p$  | $r$  | $p$  |
| BDI sum score            | $-0.096$ | $0.380$ | $-0.228$ | $0.036$ | $-0.036$ | $0.744$ | $-0.097$ | $0.379$ |
| CAARS                    |                 |                 |                 |                 |
| DSM-G                    | $0.138$ | $0.210$ | $0.099$ | $0.372$ | $-0.032$ | $0.771$ | $0.087$ | $0.433$ |
| DSM-IA                   | $0.170$ | $0.123$ | $0.188$ | $0.087$ | $0.116$ | $0.292$ | $0.197$ | $0.073$ |
| DSM-HYI                  | $0.047$ | $0.671$ | $-0.051$ | $0.647$ | $-0.141$ | $0.201$ | $-0.088$ | $0.428$ |
| IA/ME                    | $0.088$ | $0.425$ | $0.124$ | $0.260$ | $0.063$ | $0.566$ | $0.059$ | $0.592$ |
| HY/RE                    | $0.033$ | $0.767$ | $0.035$ | $0.752$ | $-0.243$ | $0.026$ | $-0.141$ | $0.200$ |
| IMP/EL                   | $0.149$ | $0.175$ | $0.060$ | $0.586$ | $-0.015$ | $0.892$ | $0.081$ | $0.465$ |
| SC                       | $-0.091$ | $0.413$ | $-0.045$ | $0.686$ | $-0.018$ | $0.872$ | $-0.015$ | $0.891$ |
| ADHS-Index               | $-0.032$ | $0.772$ | $-0.012$ | $0.916$ | $-0.041$ | $0.712$ | $0.042$ | $0.705$ |

$N=85$

Statistical significance value for these tests was set at 0.0125

BDI Beck depression inventory

CAARS the Conners’ adult ADHD rating scale

DSM-G DSM-IA and DSM-HYI: three subscales of CAARS consisting DSM-IV ADHD symptoms

IA/ME inattention/memory

HY/RE hyperactivity/restlessness

IMP/EL impulsivity/emotional lability

SC self-concept
No change in mean LRTC due to pharmacological intervention

After a 4-week intervention with extended release methylphenidate, no significant changes in mean LRTC in corresponding EEG frequency bands were observed in the entire population, nor within the ADHD+ or ADHD- groups. Interestingly, the effect sizes for change due to intervention in mean delta-, theta- and beta-LRTC was slightly larger in the ADHD- than in the ADHD+ group (delta of 0.045 vs. 0.035; theta of 0.162 vs. 0.117; alpha of 0.323 vs. 0.099; beta of 0.216 vs. 0.163). There was no clear indication that ADHD- and ADHD+ group different regarding the LRTC-difference between baseline and final visit (supplementary file Table S3). The corresponding detailed statistical results are consolidated in Table 3. An overview of the topographical distribution and differences is provided in Fig. 3.

The improvement in clinical symptoms due to pharmacological intervention

In the entire sample population, analyses of changes from baseline to final visits revealed a significant improvement in depressive (BDI, MADRS) and ADHD symptoms (CAARS). This improvement was in accordance with improvement in other clinical symptoms (CGI-S) as well as in interpersonal conflicts (IIP) and increased quality of life (WHOQOL-BREF) measured by questionnaires. Refer to Table 1 for a summary of the results.

The similar significant improvement was obtained in the ADHD+ and the ADHD- groups: patients in the ADHD+ group showed significant improvements in all investigated measurements. Likewise, patients in ADHD- group showed significant improvements in their existing symptoms, i.e. all investigated measurements except BDI. Patients in the ADHD+ group had slightly larger effect sizes than patients in the ADHD- group for CGI-S (0.863 vs. 0.781), MADRS (0.465 vs. 0.396), IIP (0.630 vs. 0.392) and WHOQOL-BREF (–0.548 vs. –0.383). Additionally, effect sizes for differences in scores of CAARS subscale DSM-IA (0.796 vs. 0.793), DSM-HYI (0.785 vs. 0.772), IA/ME (0.852 vs. 0.768), HY/RE (0.852 vs. 0.837) and IMP/EL (0.839 vs. 0.728) between baseline and final visit were slightly larger in ADHD+ than in ADHD- group. However, these two groups did no differ significantly regarding these differences between baseline and final visit (supplementary file Table S3).

Discussion

The first aim of this study was to examine the presence of LRTC in adult patients with ADHD and to investigate their treatment-related changes. As a second aim of this study, we
compared LRTC, severity of clinical symptoms and status between comorbidly depressed and non-depressed aADHD patients. We also investigated to which extend the effect of pharmacological interventions with psychostimulants was influenced by the additional depressive symptoms.

To the best of our knowledge, this is the first study that demonstrated the presence of LRTC in aADHD. Significant LRTCs were observed across all investigated EEG frequency bands. LRTCs are considered to reflect the developmental trajectories of human brains from childhood to adolescence, during adolescence and even up to early adulthood after which the temporal structure stabilizes [36]. Previous studies suggested that synaptic pruning extends well into adolescence [53, 54], and altered synaptic pruning is associated with those neurodevelopmental disorders that have prominent early onsets such as autism, ADHD and schizophrenia [55–57]. Moreover, the findings about attenuated LRTC in alpha and beta oscillations in schizophrenia [34, 58] and autism [59] indicated that there might be unusual rapid changes among different neural states in these patients, which was previously hypothesized to attribute to increased variabilities of neuronal activities [34]. Given the symptom overlaps between schizophrenia/autism and ADHD, it is reasonable to surmise that the aberration of the LRTC (very likely an attenuation) may as well be observed in aADHD when compared to healthy controls. This issue should be raised further in future studies.

Twenty-eight out of 85 of our aADHD patients reported additional depressive symptoms at baseline, which resulted in a prevalence of comorbid depression of about 33% in this study. Notably, this is not a representative prevalence since the patients with acute episodes of major depression according to ICD-10 criteria were already excluded during patient screening. Nevertheless, our aADHD patients reported depressive symptoms based on BDI-II. These patients did experience more difficulties in diverse interpersonal domains, perceived lower quality of life and showed worse self-concept as well as more emotional impulsivity (see Table 1) than those without depressive symptoms.

Interestingly, in this study, depressed aADHD patients also reported severe ADHD symptoms already in childhood based on a subjective retrospective diagnosis (see Table 1), which implies a positive relationship between the severity of ADHD symptoms and the occurrence of comorbid major depression or further aggravation of ADHD-related features. These findings are supportive of results from a recent retrospective longitudinal study based on a German population, in which authors emphasized the positive influence of early recognition of ADHD on the prevention of development and aggravation of comorbid mental illnesses [60].
As above-discussed, our depressed aADHD showed further impairments due to the additional depressive symptoms, such further impairment on LRTCs is potentially reflected by the negative, but non-significant correlation between theta-LRTC and severity of depressive symptoms ($r = -0.228$, $p = 0.036$) and slight attenuated theta-LRTC in depressed
aADHD with a small effect size (Ir= 0.191). Our findings, however, are in inconsistence with previous results reporting higher values of theta-LRTC in diagnosed depressed patients [32, 42]. In interpreting this discrepancy, it is important to mention that we excluded patients with moderate and severe depressive episode during patient screening. Our remaining aADHD patients, unlike typical depressive patients with increased persistence of maladaptive thinking, showed tendencies towards rapid mood changes and moment-to-moment dynamics in behavior due to emotional lability and hyperactivity/impulsivity, respectively.

In our entire sample population, there was an overall improvement in scores of all utilized ADHD symptom assessments at the final visit compared to the scores at baseline, after receiving extended release methylphenidate as monotherapy for 4 weeks (Table 1). These results suggest that the core symptoms of most of aADHD were reduced following treatment with methylphenidate with some of the patients (about 30%) even reaching therapy remission. The description and discussion of these results has already been published elsewhere [44].

In the present study, we mainly focused on the moderating effect of additional depressive symptoms on the treatment effect on ADHD symptoms. It is not surprising, that the majority of patients reported decreased depressive symptoms after treatment with methylphenidate, as the intake of methylphenidate has been shown to lead to amongst others increased extracellular dopamine levels [61], which has been proven a deficit in at least subgroups of depression [62]. Regarding the symptom comparison at baseline, our depressed aADHD presented more severe dysfunctions than non-depressed aADHD patients did. This remained the same at the final visit, with depressed aADHD patients still reporting more severe symptoms than those with ADHD only. This might indicate that depressed aADHD benefited from the treatment to the same extent as non-depressed aADHD did. This could be confirmed by the statistical results regarding the extend of changes in ADHD relevant symptoms (Table S3 supplementary file). However, the effect sizes for treatment induced symptom changes were slightly larger in global clinical impression (0.863 vs. 0.781) and depressive symptoms by external assessment (0.465 vs. 0.396), and were larger in interpersonal conflicts (0.630 vs. 0.392) and quality of life (−0.548 vs. −0.383) in our depressed aADHD patients. These findings implied that, though receiving the same treatment and same extents of changes in clinical symptoms, our depressed aADHD patients subjectively experienced more benefits from treatment with methylphenidate, above all in in domains of interpersonal relationships and quality of life.

In contrast to our expectation, no changes of LRTC were observed after 4-week monotherapy with methylphenidate (Fig. 3). Different from the result of this study, Gärtner et al. [32] demonstrated, after a brief treatment with either mindfulness meditation or stress reduction training for 2 weeks, a reduction of aberrant theta-LRTC in depressed patients. Similarly, through a close-loop stimulation neuro-feedback treatment, alpha-LRTC was enhanced in healthy controls under resting conditions [63] or suppressed in patients with post-traumatic stress disorder [38]. On the other hand, in a sample on 21 non-comorbidly depressed aADHD patients, who received therapy with methylphenidate, the maintenance of normalization of EEG power normalization in theta band had been confirmed in a range from 0.5 to 7 months and its change in rest-to-task transition effects revealed to be moderately correlated with the dose of methylphenidate [64]. All these results convey a consensus: though there is preliminary evidence for the heritability [65] and high temporal stability of LRTC [22], its effect might possibly be achieved or registered by interventions acting wide distributed effect on brain or requiring joint coordination among different networks. Given evidence that the strength of LRTC increased while EEG power decreased [36], it would be of interest whether the theta-LRTC as well as theta power could also be influenced by methylphenidate when certain doses and duration of treatment is reached. Unfortunately, we are not able to provide estimations on this based on the results of the current study. This issue should be studied further.

Would LRTC serve as a trait or as a state marker? As we described in Introduction, LRTC reflects the adaptability to maintain the balance between stability and flexibility of neuronal assemblies. An imbalance between stability and flexibility could be found in different psychiatric disorders, and this imbalance can be expressed through either increased or reduced LRTC, when compared to a control group in each study. Similar findings could be found in the study of Gärtner et al. [32] in sample of patients with depression, they found changes in LRTC after the intervention, this change associated with improvement in symptomatology. In this sense, LRTC could contain both trait and state aspects. However, in this study, the finding about no change in LRTC after 4-week medication seems to indicate that, the LRTC contains trait characteristic. In contrast, there was also study [66] demonstrated that LRTC changed/reduced after 40-h sleep deprivations. This finding seems to indicate the state aspect of LRTC. Whatever, to this issue more research is necessary and worthwhile.

Some limitations of this study need to be mentioned: a lack of control sample in this study prevents us to draw a conclusion on the role of LRTC, especially in regards to alpha and theta oscillations in the pathological mechanisms underlying ADHD and comorbid depressive disorder. We cannot be certain that the observed changes are linked directly to methylphenidate due to the lack of placebo control group. Also, the relatively short duration of treatment increases the difficulty for us to detect the effect; particularly
because many patients did not reach the target dose due to side effects [44]. Additionally, the trait and state characteristics of LRTC should be considered during data collection and analyzing. Findings of existing researches supplied vague and inconsistent results; there is both evidence for trait [32] and state [66] aspects of LRTC. Although the current study has taken this issue already into account and kept the first 10 min of the total 15 min resting EEG to reduce the CNS arousal effect, there is so far no uniform standard when LRTC is analyzed. In further studies, these limitations should be considered and probably controlled.

In conclusion, the current results provide direct evidence for the presence of LRTC in adult patients with ADHD. Different from typical patients in depressive episode in context of a major depression disorder, our remaining depressed aADHD patients showed due to emotional lability and hyperactivity/impulsivity tendencies toward rapid mood changes and moment-to-moment dynamics in behavior. The impact of additional depressive symptoms could be clearly obtained based on comprehensive evaluation about clinical relevant symptoms but potentially in temporal structure quantified by the LRTC in different frequency band of neural oscillations. This study failed to show changes in LRTC following treatment with extended release methylphenidate. However, our depressed ADHD patients did seem to experience more benefits from the therapy based on self-reports.

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Author contributions J.H., M.S., and M.G. conceived and designed the study. J.H. and M.G. analyzed data. J.H., M.S., and M.G. interpreted data and critical revision of this manuscript. J.H. wrote the manuscript. J.H., M.S., and M.G. edited the paper. All authors have contributed to and approved the final manuscript.

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Data availability The data set supporting the conclusions of this article are included within the article. The spreadsheets and corresponding syntax are available on request from the first author.

Declarations

Conflict of interest MS has received speaker’s fees from Lilly, MEDICE Arzneimittel Pütter GmbH & Co. KG, Servier and was an advisory board member for Shire/Takeda. AR has received speaker’s honoraria and/or served on advisory boards for MEDICE, Shire/Takeda, Janssen, neuraxpharm, Sevier and SAGE. SKS received author’s, speaker’s and consultant’s honoraria from MEDICE and Shire/Takeda. EA was an advisory board member for Shire/Takeda. JG has received research funding from the German Federal Ministry of Education and Research, German Science Foundation, and speaker fees from Sanofi, Lundbeck, Janssen-Cilag, Lilly and Otsuka. UH has received funding from, and was a consultant for MEDICE and an advisory board member for Janssen-Cilag. The other authors do not report any possible conflicts of interest.

Ethics declarations This study was carried according to the Declaration of Helsinki and the Guideline for Good Clinical Practice. This study was proved by local ethics committee of the University of Leipzig (337/15-ff). All participants signed an informed consent.

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