Epilepsy & Behavior 75 (2017) 60–65

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Increased rates of intermittent rhythmic delta and theta activity in the electroencephalographies of adult patients with attention-deficit hyperactivity disorder

Dominique Endres [a,*], Simon Maier [a], Bernd Feige [a], Nora Bel Mokhtar [a], Kathrin Nickel [a], Peter Goll [a], Simon A. Meyer [a], Swantje Matthies [a], Dieter Ebert [a], Alexandra Philipsen [b], Evgeniy Perlov [a,c,1], Ludger Tebartz van Elst [a,1]

[a] Section for Experimental Neuropsychiatry, Department of Psychiatry, Faculty of Medicine, University of Freiburg, Hauptstr. 5, 79104 Freiburg, Germany
[b] Medical Campus University of Oldenburg, School of Medicine and Health Sciences, Psychiatry and Psychotherapy — University Hospital, Karl-Jaspers-Klinik, Hermann-Ehlers-Str. 7, 26160 Bad Zwischenahn, Germany
[c] Clinic for Psychiatry Luzern, Schafmattstrasse 1, 4915 St. Urban, Switzerland

ARTICLE INFO

Article history:
Received 28 January 2017
Revised 22 April 2017
Accepted 30 June 2017
Available online 19 August 2017

Keywords:
ADHD
EEG
Adults
IRDA
IRTA
LANI

ABSTRACT

Introduction: Adult attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. In subgroups of patients with a (para)epileptic pathomechanism, this might be due to intermittent rhythmic delta or theta activity (IRDA/IRTA).
Participants and methods: Using a fully data-driven analysis, we compared the IRDA/IRTA rates in the resting electroencephalography (EEG) results of 97 adult patients with ADHD and 30 control subjects. The IRDA/IRTA rates before hyperventilation (HV) and for HV difference (difference between IRDA/IRTA rate after and before HV) were compared between groups using a linear model.
Results: We detected significantly increased rates of IRDA/IRTA before HV ($F = 4.209$, $p = 0.042$) in patients with ADHD but no significant difference between the groups for HV-difference ($F = 2.46$, $p = 0.119$).
Discussion: The increased IRDA/IRTA rates before HV in the group with ADHD might lead to (para)epileptic short-term effects (e.g., impulsivity) via local area network inhibition, and to long-term effects (e.g., cognitive deficits) via connectivistic brain restructuring.

1. Introduction

1.1. ADHD in adulthood

Adult attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with prevalence rates of 2–4% [1–3]. The main symptoms are inattention, hyperactivity, impulsivity, disorganized behavior, emotional instability, and impaired affect control [1,4]. The clinical presentations of an inattentive (iADHD), hyperactive–impulsive (hADHD) and combined subtype (cADHD) can be distinguished (http://www.dsm5.org). Frequent comorbidities are depression, anxiety disorders, and addiction [1,5]. Multimodal treatment options include pharmacological interventions (most often with methylphenidate) and psychotherapy [6–10].

1.2. Pathophysiology of ADHD

Neurochemically, a dopaminergic and norepinephrinergic deficit plays a central role in the pathophysiology of ADHD [1,11]. Therefore, both stimulant treatment with the dopamine reuptake inhibitor methylphenidate and nonstimulant therapy with the norepinephrine reuptake inhibitor atomoxetine are effective [3]. Neuroanatomically, dysfunction of the prefronto-striato-thalomo-reentrant circuits was found in ADHD [12]. These circuits are modulated by the mesolimbic dopaminergic and the interacting glutamatergic system [13–15]. Electrophysiologically, a subtle neuronal network instability via local area network inhibition (LANI-hypothesis) might lead to short-term symptoms (e.g., impulsivity), and impaired neuronal function to long-term deficits (e.g., ongoing cognitive deficits) [13,16,17]. Such hypotheses

* Corresponding author at: Hauptstr. 5, 79104 Freiburg, Germany.
E-mail addresses: dominique.endres@uniklinik-freiburg.de (D. Endres), simon.maier@uniklinik-freiburg.de (S. Maier), bernd.feige@uniklinik-freiburg.de (B. Feige), kathrin.nickel@uniklinik-freiburg.de (K. Nickel), peter.goll@uniklinik-freiburg.de (P. Goll), simon.meyer@uniklinik-freiburg.de (S.A. Meyer), swantje.matthies@uniklinik-freiburg.de (S. Matthies), dieter.ebert@uniklinik-freiburg.de (D. Ebert), Alexandra.Philipsen@karl-jaspers-klinik.de (A. Philipsen), evgeniy.perlov@uniklinik-freiburg.de (E. Perlov), tebartzvanelst@uniklinik-freiburg.de (L. Tebartz van Elst).
[1] Contributed equally.

http://dx.doi.org/10.1016/j.yebeh.2017.06.039
1525-5050/

are supported by the efficacy of antiepileptic medication, especially carbamazepine, on a meta-analytic level [18].

1.3. ADHD and electroencephalography (EEG) findings

Electroencephalography (EEG) alterations in patients with ADHD are frequent. Epileptiform activity was found in about 25% of children with ADHD [19] and is therefore more frequent than the 0.5–8% reported in control groups [13]. Electroencephalography pathologies in patients with ADHD were detected mainly in sleep and sleep deprivation (97.5%) compared to 7% in wake-only records [19]. At least 20% of children with epilepsy are affected by ADHD compared to about 5% in the pediatric control population [20,21]. Epilepsy was associated especially with the inattentive subtype [21]. Most of the earlier EEG studies were performed in children with ADHD, not in adults.

1.4. Rationale for our study

Given these observations, the aim of our study was to analyze the role of EEG alterations in adult patients with ADHD as compared to a healthy control group. More precisely, we automatically analyzed the rate of intermittent rhythmic delta and theta activity (IRDA/IRTA) in a large cohort of adult patients with ADHD. IRDA/IRTA was interpreted as pathological EEG activity caused by diverse etiology, including epileptic reasons [22–24]. We earlier put forward the idea that IRDA/IRTA has the potential to induce adaptive homeostatic processes, which might lead to functional alterations of the affected neuronal networks [13,16,17,25]. We hypothesized that we would find (1) increased IRDA/IRTA rates in the resting EEGs of the group with ADHD before hyperventilation (HV) and for HV-difference (i.e., for the difference between after and before HV), and (2) significant correlations between IRDA/IRTA rates and psychometric scores of inattention.

2. Participants and methods

The study received approval from the local ethics committee (*Faculty of Medicine, Freiburg University, 217/06*). The EEG examinations in the group with ADHD were part of the clinical diagnostic routine workup. All patients and controls agreed to the EEG measurements.

2.1. Patient assessment

The recruitment of patients with ADHD took place between 2007 and 2010. Experienced senior consultant psychiatrists assessed the patients according to *DSM-IV* criteria for ADHD. Comorbid schizophrenia, bipolar disorder, borderline personality disorder, antisocial personality disorder, suicidal or self-injurious behavior, autism, motor tics, Tourette's syndrome, and substance abuse/dependence within 6 months prior to screening (not episodic abuse) led to exclusion. Positive drug screening also led to exclusion. All patients were stimulant-free for a minimum of 6 months. Patients with somatic diseases that might cause symptoms of ADHD (e.g., former inflammatory disease of the brain, epilepsy, current hyperthyroidism, etc.) were excluded. Psychometric testing included the Wender Utah Rating Scale (WURS-k) for ADHD symptoms in childhood, the Conners Adult ADHD Rating Self-Report Scale in the Long Version (CAARS-S:L) for current ADHD symptoms, and the Beck Depression Inventory (BDI) for current depressive symptoms [26–29]. The multiple-choice vocabulary intelligence test (MWT-B) was used to quantify crystallized intelligence [30,31].

2.2. Healthy control group assessment

For the creation of the control group, we carried out EEG examinations in healthy control subjects between 2011 and 2012. The control subjects were recruited via public announcements. All control subjects with relevant psychiatric, medical, or neurological diseases were excluded from the study, as well as controls taking psychotropic drugs. Controls were investigated using semi-structured interviews (i.e., Mini International Neuropsychiatric Interview) and psychometric testing [32]. The psychometrics included the CAARS-S:L, WURS-k, BDI, and MWT-B questionnaires. CAARS-t-scores ≥ 65, WURS-k scores > 30, and BDI scores > 18 led to exclusion from the study.

2.3. Study sample

The patient cohort was recruited from our special consultations for ADHD. We searched for the EEGs in our EEG database. Electroencephalographies were available for 108 patients who fulfilled all inclusion criteria. In seven cases, the time period between EEG measurement and psychometric testing was over 2 months; to avoid inaccurate psychometric scores at the time of the EEG measurement, we excluded these patients. Moreover, four EEGs were excluded due to artifacts. In so doing, we were able to collect EEG data for 97 patients. Electroencephalography examinations were performed in 34 healthy controls; one EEG was excluded due to technical reasons (i.e., too many artifacts), one EEG was excluded due to incomplete psychometrics, and two of them were excluded due to marginal but increased psychometric ADHD scores (i.e., CAARS-t-subscores > 65), resulting in a control group of 30 subjects.

2.4. EEG acquisition

Topographical EEG was recorded using all 21 standard locations of the international 10–20 system [33] along with a Schwarzer 29-channel system and the Deltamed 'Coherence' acquisition software. The recording reference was Fpz, ground Oz. Analog signals were recorded with a time constant of 0.3 s and a low pass of 70 Hz, sampled at 256 Hz, and continuously stored for further processing. Offline, the digital signals were filtered between 0.3 and 45 Hz and down-sampled to 100 Hz. Electroencephalography monitoring was performed over 11 min including (1) a resting state EEG for 6 min, (2) an HV period for 3 min, and (3) a post-HV period for 2 min.

2.5. EEG analysis

The data analysis was performed using our in-house software avg_q (*https://github.com/berndf/avg_q*). First, the software marked artifacts, including signal jumps and "blocking" (i.e., sections without signal variation in any channel). Second, the artifact-free data parts were analyzed using independent component analysis (ICA). Only the parts 5 s before and after any artifact marker were studied (extended ICA) [34,35]. Third, the detection and correction of electro-oculographic (EOG) artifacts was done by exclusion of EOG-related ICA components. In the fourth step, the IRDAs/IRTAs were detected. Therefore, empirically determined thresholds were used for the detection of jump and phase artifacts for optimizing detection and minimizing false-positive findings. IRDA/IRTA detection was done by sorting the ICA time series between 2 and 7 Hz and thresholding for maximal amplitude between 25 and 245 μV. Only IRDA/IRTA candidates within the artifact-free EEG parts were considered. IRDA/IRTA was detected in all non-excluded independent components, irrespective of topography. IRDA/IRTA rates were calculated as events per minute for the intervals before and after HV. Moreover the difference between after HV and before HV, abbreviated as "HV-difference", was computed. The method was published earlier [17].

2.6. Statistical analyses

The statistical analyses were performed using the software R, version 3.2.2 (www.r-project.org), and the Statistical Package for the Social Sciences, version 22 (SPSS 22; www-01.ibm.com/software/analytics/spss). Group comparisons for continuous variables (age, IQ,