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ALTERATIONS OF RESTING EEG GAMMA ACTIVITY IN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

PhD thesis

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List of Abbreviations

ADHD: Attention-deficit/hyperactivity disorder

$ADHD_{MPH-}$: Study subject not taking methylphenidate

$ADHD_{MPH+}$: Study subject on methylphenidate maintenance treatment

ADHD-I: Inattentive subtype of ADHD

ANOVA: Analysis of variance

ANCOVA: Analysis of covariance

AUC: Area under curve

CAARS: Conners' Adult ADHD Rating Scale

CNV: Contingent negative variation

CNS: Central nervous system

CPT: Continuous Performance Test

DAN: Dorsal attention network

DMN: Default mode network

DSM: Diagnostic and Statistical Manual of Mental Disorders

EEG: Electroencephalography

fMRI: Functional MRI

FDA: Food and Drug Administration

HC: Healthy controls

ICA: Independent component analysis

LFP: Local field potential

MEG: Magnetoencephalography

MPH: Methylphenidate

P3: P300 evoked potential

qEEG: Quantitative EEG

ROI: Region of interest

RSN: Resting-state network

SD: Standard deviation

SE: Standard error

SN: Salience network

TPJ: Temporoparietal junction

VAN: Ventral attention network

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1 Introduction

1.1 Clinical characteristics of adult attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent mental disorders in children, with an estimated worldwide prevalence rate of 5% (1). ADHD is currently considered a neurodevelopmental disorder. Its age of onset is usually around school-age, partially because of the higher demands in behavioral and cognitive functions in the educational setting. Its typical manifestations include hyperactivity, attentional disturbances (mainly short attention span, distractibility, and concentration problems), impulsivity, and rapid emotional shifts. Perceptual disturbances (hyper- or hyposensitivity), coordination problems, language, and speech deficits often co-occur, and comorbid conduct- or mood disorder is also common (2, 3).

The hypothesized etiology of the disorder was the delayed maturation of impulse inhibition which was proposed to be outgrown until adulthood. The pioneering works of Wender and colleagues (4, 5) ruled out this concept. Later, a growing interest turned toward the adult manifestations of ADHD (6). Approximately two-thirds of childhood ADHD patients exhibit the full criteria of the disorder as adults or have limited but persistent symptomatology (7-10). The adult lifetime prevalence of the disorder is 1.5-4% in the general population (11-13). Adult ADHD is also characterized by inattention, hyperactivity, and impulsivity as core symptom domains, but hyperactivity often decreases in its severity over time (14). Besides, emotional dysregulation – though also possibly present in the childhood form of the disorder – is assumed to be more typical in adults (15, 16). Therefore, emotional dysregulation is proposed as a potential fourth core symptom bundle in adults with ADHD (17).

The importance of adult ADHD for the medical community is that the unrecognized or untreated chronic, pervasive ADHD often results in unfavorable (functional) outcomes, such as higher rates of criminality (18-22), traumatic injuries (23-26), traffic accidents (27), divorce (28), unemployment (29, 30), lower education (31-33) or even higher mortality rate (34, 35). ADHD also increases the risk for psychiatric comorbidities, for instance, affective disorders (36-39), suicide (40-42), substance abuse (43-48), or pathological gambling (49, 50).

The diagnosis is based on evaluating the presence of clinical symptoms. Diagnostic criteria underwent modifications with the introduction of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) in 2013 (51). According to the previous edition of the DSM (DSM-IV-TR (52)), an individual could be diagnosed to have ADHD if s/he either had 1) 6 or more inattentive and/or 2) 6 or more hyperactive symptoms from the symptom list for at least six months, at least in two different settings of life, and with severity sufficient to induce functional impairment. In children, the age of onset must be before age seven, and the symptoms must not exclusively co-occur with the course of other mental disorders. There were three significant changes in these criteria in DSM-5 (51) compared to the DSM-IV-TR. First, the likely age of onset was increased to 12 years in children. Second, the required number of the inattentive or hyperactive symptoms was decreased to 5 in the case of older adolescents (>17 years) and adults. Third, the criterion of functional impairment was incorporated into the general definition of the core symptom domains in a simplified manner instead of handling this criterion as a distinct requirement for the diagnosis. Considering these changes, a further increase in prevalence rates is expected, resulting in an even higher unmet need regarding treatment.

Given that the clinical symptoms of ADHD overlap with other prevalent mental disorders, including mood disorders, anxiety disorders, substance abuse/dependency, or borderline personality disorder (and these are often comorbid with adult ADHD), a growing need for an objective, well-replicable biomarker has emerged in the last decades to help clinicians to create an accurate (differential) diagnosis, and to monitor the efficacy of pharmacological interventions. EEG provides a simple, fast, and comfortable noninvasive opportunity to measure direct neural activity. Thus, tremendous efforts have been invested in identifying such a quantitative EEG biomarker.

1.2 Previous EEG research in adult ADHD in the traditional frequency ranges

1.2.1 Overall background

The first EEG studies in ADHD children have already been conducted as early as the 1970-ies (53-55). EEG is henceforward widely utilized as a research tool in childhood and adult forms of ADHD. One of the standard methods for quantitative EEG analysis is the spectral decomposition of the EEG. The electroencephalogram is a complex, time-varying bioelectric signal. With the Fourier transformation, artifact-free epochs of this

complex EEG can be decomposed to frequency-dependent, quantifiable functions. The classical frequency domains to which the EEG is decomposed are the delta (<4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz) bands. Absolute power in a frequency range is the area under curve (AUC) value in the frequency bin, while relative power is the percentage of power in a frequency range relative to the total power. It is to note that apart from the spectral analysis of the resting EEG, several other methods (e.g., event-related potentials, event-related spectral perturbations, microstate analyses, etc.) are utilized in the electrophysiological research. We focus in this work on the alterations found in the spectra of resting quantitative EEG (qEEG) in ADHD patients versus controls.

1.2.2 Resting EEG alterations in adult ADHD (0.5-30 Hz)

The main alterations of resting EEG in ADHD children are elevated theta band power, decreased beta power, and elevated theta/beta ratio in patients relative to their peers (for review see (56)). Data from adult ADHD samples are less consistent. Some studies failed to detect overall differences between adult ADHD and control groups (57), or found between-group differences exclusively for the inattentive subtype of the disorder, but not for ADHD in general (58), or uncovered group differences only on data after an ICA-based transformation but not on the raw EEG (59).

Probably the most replicable resting-state quantitative EEG finding in adult ADHD is the increase of absolute (60-65) and relative (60-62, 66) theta-band power. The topographic distribution of the theta-band difference is either global- or appears over the posterior scalp regions according to studies which usually utilize sparse spatial sampling (i.e., with 19-21 measurement electrodes). Between-group differences, however, exhibit a more complex scalp topography if high-density recording systems are used. Woltering et al. (65) reported higher anterolateral-, but diminished central- and posterior absolute theta power in adult ADHD college students relative to controls. The region-specific increase observed over different cortical areas seemingly contradicts previous findings of a general theta increase in ADHD, but at the same time underlines the possible topographical differences of qEEG findings over different brain areas, thereby highlighting the importance of dense array recording devices. Gender might also play a role in the theta elevation in ADHD. In a publication by Hermens et al. (64) the absolute theta-band power

increase was present only in male ADHD subjects relative to controls but was absent in females. Similarly, to theta-band findings, absolute delta power was lower in adult ADHD than controls in several studies (60-62, 64). Other authors, however, reported decreased relative delta power (66) or failed to confirm delta-band alterations in patients relative to controls (63). Alpha-band alterations in adult ADHD have only been reported in two studies with opposite results: while Koehler et al. (63) found elevated absolute alpha power in adult ADHD, Woltering et al. reported lower absolute and relative alpha power in patients than controls (65). The decreased beta-band power is also less consistently replicated in adult studies (64, 65) or is limited to the relative beta power (60, 62). Moreover, seemingly contradictory results of elevated beta power measures have also been reported (62, 66-68). The significance of the elevated beta power in ADHD is still a question of debate. While some authors argue that these patients represent an electrophysiological subtype of ADHD (66, 69, 70), others argue that the beta elevations might be the correlates of more severe impulse control problems spanning across diagnostic categories (67). Similarly, the elevated theta/beta ratio in adults has been proposed to reflect a transdiagnostic attentional dysregulation (71) and not a typical electrophysiologic feature for ADHD, albeit increased theta/beta ratio has also been reported in the literature (60-62, 65).

1.2.3 Hypothesized mechanisms underlying the altered EEG findings in ADHD

Traditionally, EEG alterations in ADHD were explained in the context of either the developmental lag or the hypo-arousal model.

The developmental lag model (72) provides a theoretical background for lower-band (delta and theta) findings in ADHD. Specifically, children with ADHD are characterized by an age-inappropriate behavioral development (“immaturity”) manifesting in increased levels of hyperactivity relative to their healthy peers. According to the developmental lag theory, this age-inappropriateness is also reflected in the brain electrophysiology, when elevated theta or delta power are reported in ADHD, as brain maturation co-occurs with significant power reductions in the lower frequency ranges. According to the developmental lag model, the electrophysiological maturation process is compromised in ADHD. This model implied that central nervous system maturation/development is fundamentally the same in ADHD and healthy peers, but slower in patients. However, the

growing body of literature from the last two decades reporting the persistence of ADHD in late adolescence and adulthood necessitated a modification of the original theory. This was mainly because EEG findings in persistent ADHD were partially inconsistent with childhood data and could not be reassuringly explained in the context of maturational lag. Therefore, Hobbs et al. (73) proposed the developmental deviation model. According to this theory, CNS development in ADHD – at least in the persistent form – is not or not exclusively slower than in controls as hypothesized by the maturational lag model but also deviates from normality.

The hypo-arousal model (74) assumes unspecified neurodevelopmental alterations as well, which would imply a hypo-aroused state of the CNS. According to the hypo-arousal model, elevated theta-, diminished beta power, and increased theta/beta ratio in ADHD are the electrophysiological representations of central hypo-arousal, along with reduced skin conductance level, a representation of decreased peripheric arousal (55, 75, 76). On the behavioral level, the hypo-arousal is reflected by impulsive, novelty-seeking behavior.

EEG alterations in adult ADHD are often challenging to interpret in the context of the above classical models, partially due to lack of information (e.g., the adult developmental course of the EEG) or inconsistent findings (e.g., excessive beta power). Therefore, the focus of current electrophysiological research on adult ADHD was turned beyond the classical EEG bands, by concentrating on the gamma band. The next section will provide an overview of gamma-band activity and its alterations in childhood ADHD.

1.3 Gamma band activity and its associations with resting-state brain networks

1.3.1 The generation and role of gamma-band activity

The EEG gamma-band (77) ranges above 30 Hz (30-120 Hz). Of this rather broad frequency range, 40 Hz frequency is of particular interest due to its crucial role in the perceptual process, which is well-documented in the literature. One of the earliest reports of gamma activity derives from a primate study on visual perception (78). Further research revealed that stimulus-related gamma activity is evolutionary well-preserved and is present under anesthesia and unanaesthetized conditions in a large variety of species ranging from invertebrates to humans (79-84). It is also well-established that gamma synchronization is present not only during visual perception but also in every sensory

modality and during cognitive processes, including the evaluation of sensory stimuli and the preparation of behavioral responses (85, 86).

By utilizing spatially dense cortical measurements, it has also been delineated that there is a remarkable gamma-band coherence between nearby and remote cortical areas during perceptual and cognitive tasks (87, 88). The combination of the above discoveries led to an interpretation of stimulus-related gamma activity in the context of the binding problem. Specifically, gamma synchronization and gamma coherence play a significant role in associating different stimulus properties processed by different cortical areas into one unified percept and is also crucial in comparing the actual percept with previous experiences and evaluating its significance for the behavior. The exact nature of the binding process is still not clarified (89) and is out of the scope of this thesis. However, it is hypothesized that the binding (or segregation) is provided by the presence (or absence) of neural synchrony between cortical areas (binding by synchrony theory as reviewed by Singer and Gray in detail (90)).

Gamma activity is also interpreted in a broader sense in the framework of the organization of consciousness (91). According to the classical European psychopathology, the consciousness has two elements, the arousal and the content (92, 93). As discussed in detail by Negrao and Viljoen in their review (94), both elements can be interpreted in the context of cortical gamma rhythms. There is a spontaneous rhythmic activity at 40 Hz generated by reverberating thalamocortical circuits with a rostrocaudal propagation. The framework of consciousness is cortical arousal which is proposed to be generated by the „nonspecific thalamus”, the thalamic intralaminar nucleus projecting grossly to the entire neocortex and maintaining a cortical interneuron activation resulting in the desynchronized low-amplitude, high-frequency activity characteristic for consciousness and REM sleep. The intralaminar nucleus gets afferents from the brain stem and reverberating collaterals from cortical pyramidal cells and can be modulated/resetted from the sensory systems (91). Consciousness' other element, the content, is provided by the specific thalamic systems which operate with internal and external stimulus perception, processing, and evaluation. This system is also maintained by thalamocortical reverberating loops but with the participation of specific thalamic nuclei and specialized cortical areas (94). It is also of note that although cortical interneurons have a major role

in the generation of gamma rhythm, it is not exclusively generated by the cortex but also in subcortical areas, for example, the hippocampus (95) or basal ganglia (96).

1.3.2 Resting-state EEG alterations in the gamma band in children with ADHD

As a result of stimulus presentation or active cognitive processes the gamma band activity increases. Therefore, it is plausible that gamma is usually investigated during various task conditions. Gamma-band oscillatory responses (evoked and induced gamma rhythms) are task-related electrophysiological phenomena. These responses can be altered in neuropsychiatric disorders (97, 98), including ADHD (99-102).

Based on prior literature, it remains to be decided whether gamma-band power differs in adult ADHD from controls. In childhood ADHD, the data is also scarce, but prior publications exist. Barry et al. (103, 104) and Dupuy et al. (75) both found the decrease of resting-state absolute and relative gamma (35-45 Hz) power in 7-12 years old children with ADHD as compared to healthy peers. The study sample of Dupuy et al. included only girls, while the Barry study was conducted in mixed-gender samples. The topographical distribution of the group differences showed a posterior dominance in all three studies. Gamma power was negatively associated with total symptom severity in only one study (104) and was negatively correlated to the severity of inattention in all works (75, 103, 104). The interpretation of the results differed between the studies. While the two studies by Barry et al. explained the diminished gamma power in ADHD by cognitive disturbances including reduced attentional capacity, Dupuy et al. interpreted their results in the context of the hypo-arousal model of ADHD. The latter finding was supported by the reduced skin conductance level in the ADHD sample and its association with gamma power. Table 1 provides a summary of resting EEG gamma-band findings in childhood ADHD.

Table 1

Summary of resting-state EEG spectrum studies in childhood ADHD.

Study (Year)	N [a]	Age [b]	Eyes [c]	Leads [d]	Frequency band	Results
Barry (2009) (103)	50/50	8-12 y	EC	21	35-45 Hz	γ ↓ in ADHD vs. HC
Barry (2010) (104)	40/40	8-12 y	EC	19	35-45 Hz	γ ↓ in ADHD vs. HC
Dupuy (2014) (75)	40-40	7-12 y	EC	19	35-45 Hz	γ ↓ in ADHD vs. HC*

[a] ADHD/Control, [b] Age range– ADHD and control, [c] EO = Eyes open, EC = Eyes closed, [d] Number of EEG channels, HC = Healthy controls
* The study sample consisted of only girls with/without ADHD.

1.3.3 Resting-state magnetoencephalography (MEG) alterations in adult ADHD

It is of note that a magnetoencephalographic (MEG) study also examined the gamma band neural activity differences of adult ADHD and controls. In a pharmaco-MEG study by Wilson et al. (105), the effects of amphetamine salts were investigated for time estimation performance and MEG gamma (30-106 Hz) neural activity. Regarding MEG gamma activity, comparisons between pre-treatment adult ADHD patients and healthy controls revealed that ADHD had generally weaker MEG gamma activity than controls. The same result was found for all sub-bands of gamma (low gamma: 30-56 Hz, middle gamma: 64-82 Hz, high gamma: 82-106 Hz) activity. For source localization analyses, the authors defined regions-of-interests (ROI) which were hypothesized to play a role in time estimation tasks: bilateral anterofrontal cortices, bilateral prefrontal cortices, anterior cingulum, sensorimotor area. The above gamma decrease was found in all ROIs except over the right prefrontal cortex.

1.3.4 The associations of gamma-band activity and resting-state cortical networks

Resting-state neural networks were first described in 1995 by Biswal and colleagues (106), but the existence of intrinsic, "off-task" brain activity was presumed since the late 1920-ies by Hans Berger, the inventor of human electroencephalography. Resting-state fMRI networks are defined on the basis of the appearance of fixed patterns of spatial coherence, which are present without a task condition. Since their discovery, these networks have consistently and systematically been identified. As it had also been expected decades before its verification (107), active performance during task conditions increases the energy consumption of the brain only by approximately five percent. In other words, as phrased by Marcus Raichle (108), the resting brain “is never idle”. There

has been an extensive and still growing body of literature on the resting-state brain networks since the millennium.

The best electrophysiological correlates of fMRI BOLD signals are the local field potentials (LFP) which are the summations of microelectrode-measured electric activities of the neural terminals. The scalp-recorded EEG is, in fact, the summation of LFP-s and thereby also has correlates with the fMRI signals (109). Among the EEG frequency bands, delta band fluctuations, infraslow fluctuations, and gamma-band activity are of particular interest, the latter mainly due to its well-established connection with cognitive processes (110). Recent research has proposed associations between resting-state fMRI and resting-state EEG activity (111-116). Measures of resting-state network activity exhibit age-related changes (117, 118) and also vary with disease (119-123). Such alterations in the operation of the resting-state networks or the process of switching from rest to task conditions have also been proposed in ADHD (124-128).

Considering the fact, that resting-state gamma activity is altered in ADHD, these possible alterations might include task-negative dysfunctions. So far, this area has been rarely investigated but might add valuable extensions to the electrophysiological biomarker research in adult ADHD.

1.4 Electrophysiological measures of brain maturation

1.4.1 Electrophysiological changes during central nervous system maturation

The electrophysiological maturation of the central nervous system is characterized by a massive age effect on resting EEG measures (129). The neural basis of the process is related mainly to the anatomical development of the cortex. There is an increased myelinization in the early postnatal developmental period which is followed by the dominance of the extensive loss of synapses (pruning) in adolescence. In terms of EEG, total power and power measures in all classical frequency ranges (1-30 Hz) follows a non-linear decrease (129, 130) with age from child- to adulthood. Visual inspection of EEG recordings shows that the dominant frequency increases across ages until adolescence (131). There is also evidence in the literature that the EEG maturation follows a strict topographical order. More specifically, the maturation of the lower, sub-beta bands has a caudo-rostral propagation. The onset of beta activity during development occurs centrally

which is followed by a slight posterior and then a lateral progress, reaching to the anterior regions the latest (132).

There is also an interesting debate whether beta band power increases rather than diminishes over time, because of the synaptic loss during the pruning process. Beta frequency is the dominant rhythm in late adolescents and adults with eyes open, awake conditions. As there is a marked resting cortical desynchronization, beta amplitude is usually low. According to the alternative hypothesis, the synaptic pruning ultimately leads to beta power increase by the decrease in the number of synapses, which ultimately means reduced level of desynchronization relative to the pre-pruning condition (133).

1.4.2 The characteristics of EEG maturation in adult ADHD

Only a few studies investigated age-related EEG changes in the context of adult ADHD. Most papers focused on the transition period from childhood to adolescence because of the importance to the course of ADHD in terms of remitter/non-remitter status. Data on adult ADHD shows that patients' EEG recordings grossly undergo the same maturational processes from childhood to adulthood as seen in controls. Specifically, a substantial age effect indicating a marked decline in different absolute power measures is usually found (60, 134, 135), but confirmatory findings on significant group by age effects are scarce. The only exception in the literature is Poil et al. (68). These authors found that beta decrease is topographically limited to the frontal midline and bilateral posterior electrode locations in ADHD, unlike in controls, where the beta decrease is global.

As stated above, data on age-related EEG changes *in adults* are scarce. Most previous studies report data from cross-sectional studies utilizing non-overlapping age cohorts. As ADHD is a neurodevelopmental disorder which does not remit until adulthood in approximately half of the cases, it would be useful to delineate the course of electrophysiologic measures also in adulthood focusing on cohorts of patients with a continuous age distribution. This would be of special importance in the case of biomarker candidates which could help us to understand the mechanisms underlying disease persistence or changes in the clinical manifestation.

1.5 Summary and rationale

As a summary of the Introduction, we can conclude that EEG alterations from children with ADHD have been well-documented since the '70-s. During the past two decades, a growing body of literature investigated the electrophysiological correlates of adult ADHD. Unfortunately, their results are less consistent than those of the childhood literature, and - more importantly - these results are often not replicated. Several reasons can contribute to this situation including differences in EEG recording and analyses between research groups, differences in scalp region definitions used for two-dimensional topographic analyses, eyes open/eyes closed recording condition, let alone the heterogeneity of the patient study groups, etc.

The presence/absence of the visual input is important in electrophysiology studies since the eyes open/closed condition has a significant impact on qEEG power spectra and scalp topography. Previous evidence supports that qualitatively the same, but less robust differences were found in adult ADHD with eyes open versus closed (65).

Notwithstanding the previous positive findings of EEG alterations in adult ADHD relative to healthy controls reviewed above, we can still conclude that research of the traditional EEG frequencies (0.5-30 Hz) could not identify an electrophysiological biomarker unambiguously typical for ADHD. Probably the most significant achievement in the field was the FDA approval of an EEG recording system (NEBA) as an adjunctive diagnostic tool for childhood ADHD based on the theta/beta ratio alterations associated with the disorder (136). However, the approval and its interpretation for the clinical practice were criticized and debated later [130, 131] partially because more recent research proposed that theta/beta alterations rather reflect abnormalities of attentional control than hypo-arousal and might span across diagnostic categories [132-134].

The failure of traditional EEG research shifted the focus of recent works beyond the classical frequency bands including the gamma band (>30 Hz). As it was discussed earlier, resting gamma-band power was decreased in children with ADHD as well as task-positive gamma activity was found to be altered in this population relative to healthy controls. As cognitive disturbances, resting-state neural network abnormalities, and alterations in cortical development had consistently been reported in ADHD and were all related to task-positive gamma-band differences in previous study populations, our research was based on the hypothesis that gamma-band abnormalities might also be

reflected in the off-task resting condition in adult with ADHD. As ADHD is a neurodevelopmental disorder, gamma alterations might be present during the entire adult lifespan in case of disease persistence. Nevertheless, this question has never been addressed so far. Further investigations of these assumptions might provide valuable information to the field of electrophysiological biomarker research in adult ADHD.

In this thesis, EEG results derive from eyes-open recording settings with static visual input (patients were instructed to look to a fixation cross) without active participation in task conditions as we posited that this experimental setting represents the everyday off-task, scanning, readiness situation the best (137). For the recording, we used a 128 channel, high-density EEG recording system (BioSemi Active Two System, BioSemi, Amsterdam, the Netherlands) with proprietary electrode labeling and positioning with an electrode cap (for demonstration see (138)). The electrode labels are generated with the combination of a letter referring to the scalp quadrant where the electrode is located and a number ranging from 1 to 32 denoting the ordinal number of the recording channel. As the BioSemi labels and the International 10-10 labels (139) have a substantial two-dimensional spatial overlap, we provided - whenever available - both the proprietary BioSemi and the International 10-10 labels in this work. Artefact-free, 2500 ms epochs were used for Fourier transformation in order to generate power spectra. During our analyses, we focused on the low gamma band (30-48 Hz) for better comparisons with literature data on 35-45 Hz band resting gamma power in children with ADHD (75, 103, 104). The target band was divided into two symmetrical frequency bins, henceforward $gamma_1$ (30-39 Hz) and $gamma_2$ (39-48 Hz) in order to achieve higher spectral resolution.

This thesis is based on two studies, which were approved by the Scientific Research Ethics Committee of the Hungarian Medical Research Council under the respective approval identifiers TUKEB 215/2011 and TUKEB 62/2013. The studies were conducted in accordance with the Declaration of Helsinki.

2 Objectives

2.1 Objectives of the first study

Our first study aimed to investigate the alterations of resting-state EEG gamma activity in a clinically well-characterized, large group of adult ADHD patients compared to age-, gender- and education-matched healthy controls. Since the adult ADHD sample consisted of both drug-naïve and methylphenidate-treated subjects ($ADHD_{MPH-}$ and $ADHD_{MPH+}$, respectively), we stratified the patient sample by medication status, which resulted in three comparison contrasts ($ADHD_{MPH-}$ vs. controls, $ADHD_{MPH+}$ vs. controls, and $ADHD_{MPH-}$ vs. $ADHD_{MPH+}$). Because the aim was to examine gamma alterations associated with ADHD, the focus of the analysis was the comparison of the $ADHD_{MPH-}$ group with healthy controls. A second goal was to investigate the relation between gamma power and symptom severity. The third goal was that by using a high-density EEG recording system, we wanted to delineate the topographical distribution of group differences of resting gamma-band activity with a channel-wise spatial repeated-measures analysis of covariance (ANCOVA) approach. We hypothesized that 1) resting-state EEG gamma band (30-48 Hz) power would be decreased in adult ADHD compared to controls, 2) gamma power would be negatively correlated with symptom severity, and 3) significant group differences would be localized over scalp areas which correspond to cortical areas proposed to play a role in the pathogenesis of ADHD symptoms.

2.2 Objectives of the second study

Although ADHD is considered a lifelong neurodevelopmental disorder, it remains unknown whether the EEG gamma-band power reduction found in cross-sectional studies persists in the adult form of the disorder throughout the lifespan. In the second study, we aimed to conduct exploratory analyses on the data sets recorded during the first study to delineate EEG gamma-band trajectories in adult ADHD patients and controls. In our statistical analyses, we contrasted the null-hypothesis of no diagnostic group difference against the alternative hypothesis that the developmental trajectory of the gamma activity in adult ADHD patients is altered as compared to controls. Given the exploratory nature of the second study, no specific assumption about the direction and time-course of the difference was posited.

3 Results

3.1 Demographical and clinical characteristics

3.1.1 Demographics

No significant study group differences were found regarding age, gender, and level of education. Approximately two-thirds of the study sample consisted of males and approximately half of the study subjects had higher than a high-school degree. The mean age was slightly above 30 years. No significant group differences were found in mean age. The demographical and clinical characteristics of the study sample are summarized in Table 2.

3.1.2 Clinical characteristics

Significant main effect of group was found for all Conners' Adult ADHD Rating Scale (CAARS) subscale measures (Table 4). Compared to the controls, both ADHD patient subgroups ($ADHD_{MPH-}$ and $ADHD_{MPH+}$) had significantly higher overall symptom severity (CAARS total score, $F=71.02$, $p<0.0001$), core symptoms severity (CAARS Core symptom total score, $F=70.95$, $p<0.0001$), inattention (CAARS Inattention/memory problems scale, $F=66.53$, $p<0.0001$), hyperactivity (CAARS Hyperactivity/restlessness scale, $F=32.67$, $p<0.0001$), impulsivity (CAARS Impulsivity/emotional problems, $F=36.72$, $p<0.0001$) and affective symptoms (CAARS Problems with self-concept, $F=20.43$, $p<0.0001$). Hyperactivity was significantly higher in $ADHD_{MPH+}$ than in $ADHD_{MPH-}$ (CAARS Hyperactivity/restlessness scores 23.21 vs. 19.21, respectively, $p=0.0449$) while $ADHD_{MPH-}$ were significantly more inattentive than $ADHD_{MPH+}$ (CAARS Inattention/memory problems scores 26.95 vs. 22.04, respectively, $p=0.0181$). Other symptom dimensions, total core symptom severity, and overall symptom severity did not differ statistically between the patient subgroups (all $p>0.05$)

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Table 2

Basic demographics and clinical characteristics. Unadjusted p-values listed in this table remain significant after adjusting for multiple testing.

Characteristic	ADHD (N=42)		Control (N=59)	Statistics	
	MPH- (N=25)	MPH+ (N=17)		F/χ^2	p
Male, N (%)	20 (80.0)	13 (76.4)	44 (74.6)	0.28[a]	0.87
Education, High school graduate, N (%)	12 (48.0)	12 (70.6)	33 (55.9)	2.11[a]	0.35
Age, years (Mean, SD)	32.28 (10.4)	28.94 (11.4)	30.88 (11.0)	0.47[b]	0.62
Median age, years (IQR[c], Min-max)	29 (25-38, 19-57)	25 (21-35, 18-56)	27 (24-33, 19-59)	1.93[d]	0.38
Conners' Adult ADHD Rating Scale					
Total score (Mean, SD)	118.62 (22.5)	103.52 (26.1)	48.33 (27.8)	71.02[b]	<0.0001
Core symptom total score (Mean, SD)	66.27 (12.8)	62.10 (15.1)	29.1 (14.8)	70.95[b]	<0.0001
Hyperactivity/restlessness (Mean, SD)	19.21 (6.3)	23.21 (6.6)	10.82 (6.0)	32.67[b]	<0.0001
Inattention/memory problems (Mean, SD)	26.95 (4.8)	22.04 (6.9)	9.87 (6.9)	66.53[b]	<0.0001
Impulsivity/emotional problems (Mean, SD)	20.11 (7.2)	16.84 (6.2)	8.40 (5.2)	36.72[b]	<0.0001
Problems with self-concept (Mean, SD)	11.56 (5.0)	8.67 (5.3)	4.49 (4.2)	20.43[b]	<0.0001

[a] χ^2-test, χ^2

[b] ANOVA, F

[c] IQR: Interquartile range

[d] Kruskal-Wallis test, χ

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3.1.3 The age distribution of the study sample

The median age of the whole study sample was 27 years (29, 25, and 27 years in the $ADHD_{MPH-}$, $ADHD_{MPH+}$, and control groups, respectively). The study sample was not uniformly distributed (Figure 1). Since too few or too high number of subjects in any age group might influence the results of a trajectory analysis, we investigated whether there was a significant difference in the frequency distribution of our sample by younger, intermediate and older age groups. Cut-off values of the age groups were created close to the age quartiles of the whole study sample. No significant difference (χ^2=0,2354, df=2, p=0.89) was found in the distribution of age groups (younger (< 25 years old), intermediate age (25-35 years), and older (> 35 years old)) between ADHD and controls. Our results also showed that approximately 28.6% and 26.2 % of the entire ADHD sample ($ADHD_{MPH-}$ and $ADHD_{MPH+}$), and 30.5 % and 22% of healthy controls fell in the younger (< 25 years age) and older (> 35 years) age groups, respectively. In other words, a total of 54.8 % of the whole ADHD- and 52.5 % of the controls sample were outside the intermediate age range. Proportions are summarized in a tabular form in Table 3.

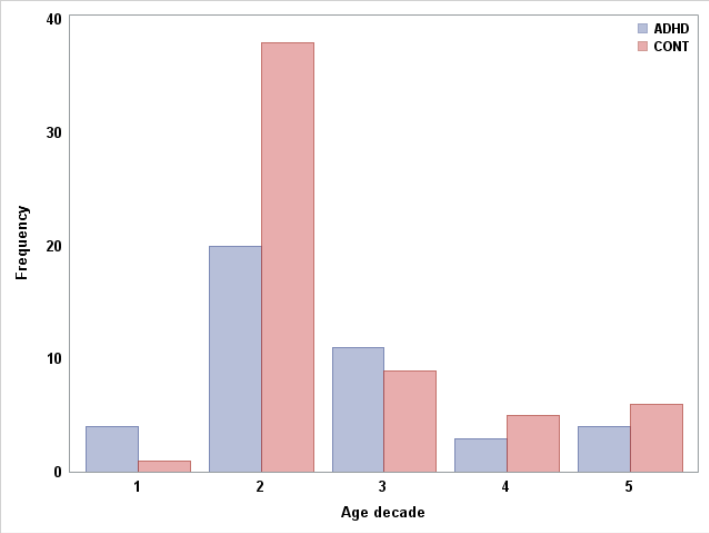

Figure 1

Age distribution of the study sample by age decades. Blue bars depict the frequency of ADHD subjects within a decade, while red bars depict the same in controls.

Table 3

The proportion of young (<25 years), intermediate aged (≥25 and ≤35 years), and older subjects (>35 years) in the sample. χ^2 test indicated no significant difference (χ^2=0.2354, df=2, p=0.89) between the study groups in the proportion of young (<25 years), intermediate aged (≥25 and ≤35 years) and older (>35 years) subjects.

Group	<25 years (N, %)	25-35 years (N, %)	>35 years (N, %)
ADHD (n=42)	12 (28.6)	19 (45.2)	11 (26.2)
Control (n=59)	18 (30.5)	28 (47.5)	13 (22.0)

3.2 Results of the first study

3.2.1 Group differences in gamma-band activity

The overview of electrode clusters with significant group differences (Control vs. $ADHD_{MPH-}$, Control vs. $ADHD_{MPH+}$ and $ADHD_{MPH-}$ vs. $ADHD_{MPH+}$) is summarized in Table 6 at the end of this section.

3.2.2 Control versus $ADHD_{MPH-}$

3.2.2.1 $Gamma_1$ band

Results are summarized in Table 4.

Channel-wise spatial repeated measures ANCOVA in the $gamma_1$ band (30-39 Hz) revealed 23 of 128 channels with significant main effect of group when comparing Controls with $ADHD_{MPH-}$ after adjusting for multiple comparisons. Significantly lower $gamma_1$ activity was found in $ADHD_{MPH-}$ than in controls.

Topographical analysis of the results showed that 19 of the 23 electrodes identified by the main effect analysis formed three scalp clusters: a right anterofrontal (Cluster A: C9[.], C10[AFF6h], C14[AF4h]), a right central (Cluster B: B18[CCP4h], B21[.], B22[C4], B30[.], B31[FC4]) and an extended right posterior (Cluster C: B9[PO10], B10[.], B11[P8], B12[.], B13[P6], B14[TP8], B15[.], B16[CP6], B24[C6], B25[.], B26[T8]) cluster (Figure 2, page 24).

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Table 4

Means (standard deviations) of $gamma_1$ (30-39 Hz) activity in the identified electrode clusters in the comparison of Control vs. $ADHD_{MPH-}$ groups by EEG electrodes. For the identification of individual EEG electrodes, BioSemi labels are used, but 10-20 system labels are also provided between square brackets if there is an appropriate corresponding electrode. Unadjusted p-values listed in this table remain significant after adjusting for multiple testing. Summary of group statistics and effect size in terms of Cohen's D is also provided. The table is based on Table 2 of reference (140).

Region and electrode	**$ADHD_{MPH-}$**	**Control**	**F**	**p**	**Effect size**
Cluster A					
C9[.]	0.65 (1.18)	1.63 (0.53)	34.69	<0.0001	1.14
C10[AFF6h]	0.82 (0.86)	1.37 (0.39)	19.79	<0.0001	0.87
C14[AF4h]	0.77 (0.52)	1.00 (0.37)	10.19	0.0001	0.52
Cluster B					
B18[CCP4h]	0.36 (0.25)	0.56 (0.28)	17.46	<0.0001	0.75
B21[.]	0.40 (0.22)	0.54 (0.34)	7.9	0.0007	0.48
B22[C4]	0.42 (0.20)	0.67 (0.60)	9.5	0.0003	0.62
B30[.]	0.73 (0.47)	1.03 (0.58)	10.43	<0.0001	0.59
B31[FC4]	0.58 (0.36)	0.82 (0.44)	11.32	<0.0001	0.61
Cluster C					
B9[PO10]	0.56 (0.61)	1.28 (0.98)	24.29	<0.0001	0.90
B10[.]	0.84 (1.04)	1.21 (0.56)	8.44	0.0005	0.47
B11[P8]	0.87 (0.63)	1.15 (0.46)	7.9	0.0007	0.52
B12[.]	0.63 (0.53)	0.90 (0.34)	12.1	<0.0001	0.62
B13[P6]	0.52 (0.37)	0.78 (0.29)	24.0	<0.0001	0.77
B14[TP8]	0.72 (0.69)	1.43 (0.76)	31.15	<0.0001	0.98
B15[.]	0.68 (0.51)	1.19 (0.41)	42.77	<0.0001	1.10
B16[CP6]	0.55 (0.55)	0.96 (0.36)	21.91	<0.0001	0.87
B24[C6]	0.75 (0.65)	1.25 (1.07)	10.26	<0.0001	0.58
B25[.]	0.90 (0.87)	1.54 (0.99)	12.94	<0.0001	0.68
B26[T8]	0.87 (1.00)	1.71 (1.08)	16.83	<0.0001	0.80

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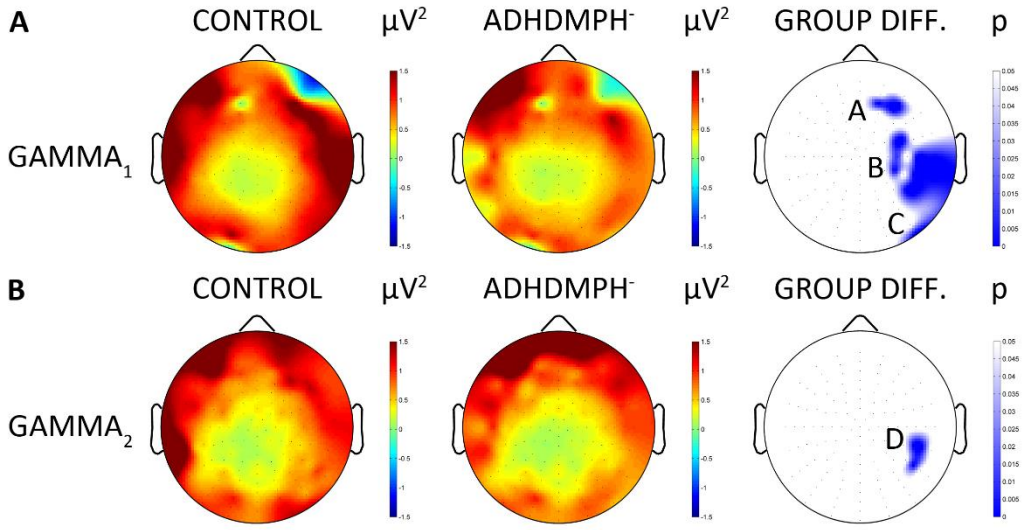

Figure 2

Scalp distribution of gamma$_1$ and gamma$_2$ activity and spatial distribution of p-values referring to their differences in the comparison of Control vs. ADHD$_{MPH-}$ groups.

Panel A depicts the topographical maps for gamma$_1$ (30-39 Hz), while panel B shows the same for gamma$_2$ (39-48 Hz) power. Color coding represents the magnitude of power values, warmer color corresponding to higher power values. Spatial distribution of group differences is provided in the third column, with darker shades of blue representing bigger group differences.

Three electrode clusters labeled by capital letters are identified in panel A: A, anterofrontal; B, right central; C, extended right posterior. Gamma$_1$ power was smaller in ADHD$_{MPH-}$ than in controls in all clusters.

One, right centroparietal electrode cluster is identified in panel B labeled with D. ADHD$_{MPH-}$ had diminished gamma$_2$ activity then controls in cluster D.

Figure 2 is based on Figure 1 of reference (140)

3.2.2.2 Gamma$_2$ band

The main effect of group was significant in 9 of 128 electrodes after adjusting for multiple comparisons when comparing Controls with ADHD$_{MPH-}$. Gamma$_2$ (39-48 Hz) was lower in ADHD$_{MPH-}$ than in controls. See Table 5 for an overview.
Three of the nine electrodes identified by the main effect analysis were localized in a right centroparietal cluster (Cluster D: B12[.], B15[.], B16[CP6]) (Figure 2).

Table 5
Means (standard deviations) of gamma$_2$ (39-48 Hz) activity by EEG derivation in the D Cluster. Electrodes are labeled with BioSemi labels – and where appropriate – with 10-20 labels between squared brackets. Unadjusted p-values listed in this table remain significant after adjusting for multiple testing. Summary of group statistics and effects size in terms of Cohen's D is also provided. Primary contrast (Control vs. ADHD$_{MPH-}$). The table is based on Table 3 of reference (140)

Electrode	ADHD$_{MPH-}$	Control	F	p	Effect size
Cluster D					
B12[.]	0.40 (0.11)	0.54 (0.25)	11.99	<0.0001	0.72
B15[.]	0.54 (0.15)	0.73 (0.34)	15.21	<0.0001	1.02
B16[CP6]	0.42 (0.13)	0.59 (0.30)	13.95	<0.0001	0.89

3.2.3 Control versus ADHD$_{MPH+}$

3.2.3.1 Gamma1 band

Channel-wise spatial repeated-measures ANCOVA identified 26 of 128 channels with significant group effect in the gamma$_1$ (30-39 Hz) band when comparing ADHD$_{MPH+}$ and healthy controls (Control vs. ADHD$_{MPH+}$) Gamma$_1$ power was significantly lower in ADHD$_{MPH+}$ than in controls.
According the spatial analysis, 19 of these 26 channels composed two electrode clusters: a right hemispheric temporoparietal (B3[CPP4h], B4[P4], B6[.], B13[P6], B14[TP8], B15[.], B18[CCP4h], B21[.], B24[C6], B31[FC4]) which exhibited partial overlap with Cluster C (the extended right posterior cluster) from the Controls versus ADHD$_{MPH-}$ comparison, and a frontocentral one around the midline (C2[FC2], C4[F4], C11[FFC2h],

C12[F2], C13[AFF4h], C21[Fz], C22[.], C23[FCz], C25[F1]) (see Table 6 on page 30 for summary).

3.2.3.2 Gamma$_2$ band

We found 25 of 128 channels with significant group effect in the gamma$_2$ (39-48 Hz) band when analyzing the Control vs. ADHD$_{MPH+}$ comparison. Again, gamma$_2$ power was diminished in ADHD$_{MPH+}$ relative to controls.

Of these 25 channels, 16 (A2[.], B1[.], B14[TP8], B15[.], B16[CP6], B19[.], B21[.], B22[C4], B23[.], B30[.], B31[FC4], C2[FC2], C3[FFC4h], C11[FFC2h], C12[F2], C22[.]) formed a large, right hemispheric fronto-centro-parietal cluster which includes 2 of the 3 channels (B15[.], B16[CP6]) of Cluster D from the Controls versus ADHD$_{MPH-}$ comparison, and also had a partial overlap with the cluster found in the comparison of Controls versus ADHD$_{MPH+}$ in the gamma$_1$ band (see Table 6 for summary).

Gamma activity and p-value maps for group differences are illustrated in Figure 3.

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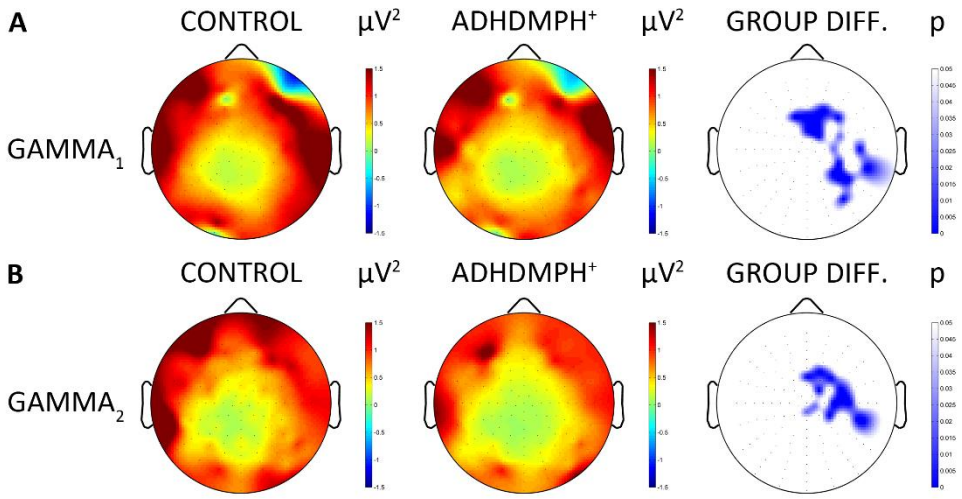

Figure 3

Scalp distribution of gamma$_1$ and gamma$_2$ activity and p-value maps of group differences when comparing Control vs. ADHD$_{MPH+}$.

Panel A depicts the topographical maps for gamma$_1$ (30-39 Hz), while panel B depicts the same for gamma$_2$ (39-48 Hz) power. Color coding represents the magnitude of power values, with warmer colors corresponding to higher power values. Spatial distribution of group differences is provided in the third column, with darker shades of blue representing greater group differences.

Gamma$_1$ power was lower in ADHD$_{MPH+}$ than controls in the midline, right frontocentral, and right parietotemporal channels (panel A). Gamma$_2$ was also lower in ADHD$_{MPH+}$ relative to controls in the right frontocentral electrodes (panel B).

Figure 3 is based on Supplemental figure S1 of reference (140)

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3.2.4 $ADHD_{MPH-}$ versus $ADHD_{MPH+}$

3.2.4.1 $Gamma_1$ band

In the comparison of $ADHD_{MPH-}$ and $ADHD_{MPH+}$ groups, 16 channels were identified with significant group effects. $Gamma_1$ power was significantly decreased in $ADHD_{MPH+}$ relative to $ADHD_{MPH-}$.

Topographical analysis identified a frontocentral midline cluster anterior to the vertex consisting of 12 of the 16 channels with significant group effect (A2[.], B1[.], C1[FCC2h], C2[FC2], C11[FFC2h], C12[F2], C21[Fz], C22[.], C23[FCz], C24[FFC1h], C25[F1], D1[FCC1h]) which was in partial overlap with the anterior cluster found in the Control vs. $ADHD_{MPH+}$ comparison (see Table 6 on page 30 for summary).

3.2.4.2 $Gamma_2$ band

Eight channels with significant group effects were found in the $gamma_2$ band when comparing $ADHD_{MPH-}$ with $ADHD_{MPH+}$. $ADHD_{MPH+}$ had significantly lower $gamma_2$ activity than $ADHD_{MPH-}$.

Of these eight channels, 3 (D8[FT7], D22[.], D25[.]) were located in a small, left frontotemporal cluster (see Table 6 for summary).

Gamma activity and p-value maps of group differences for the $ADHD_{MPH-}$ versus $ADHD_{MPH+}$ comparison are illustrated in Figure 4

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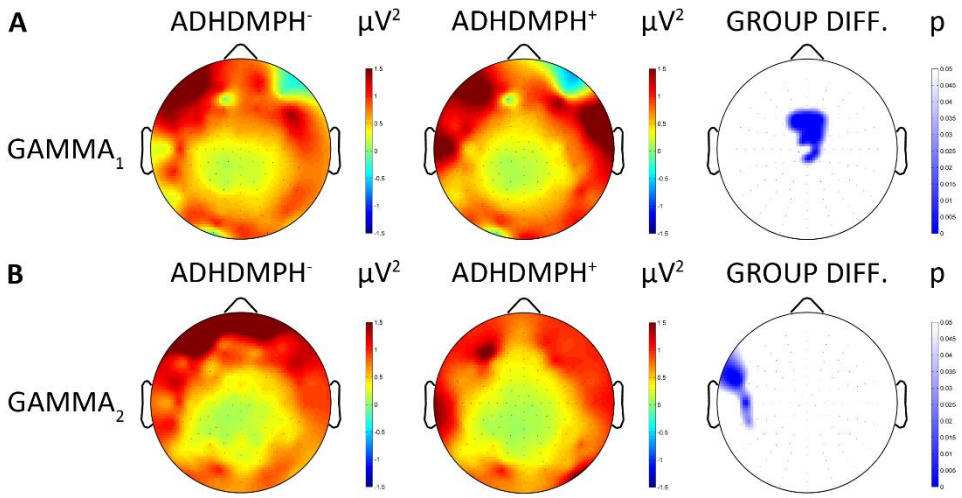

Figure 4

Scalp distribution of gamma$_1$ and gamma$_2$ activity and p-value maps of group differences when comparing ADHD$_{MPH-}$ vs. ADHD$_{MPH+}$.

Panel A depicts the topographical maps for gamma$_1$ (30-39 Hz), while panel B depicts the same for gamma$_2$ (39-48 Hz) power. Color coding represents the magnitude of power values, with warmer colors corresponding to higher power values. Spatial distribution of group differences is provided in the third column, with darker shades of blue representing more significant group differences.

Gamma$_1$ power was lower in ADHD$_{MPH+}$ than in ADHD$_{MPH-}$ in midline frontocentral electrodes (panel A). Gamma$_2$ power was also decreased in ADHD$_{MPH+}$ compared to ADHD$_{MPH-}$ in left frontotemporal derivations (panel B).

Figure 4 is based on Supplemental figure S2 of reference (140)

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Table 6

Overview of electrode clusters with significant group differences. Clusters of the Controls vs. $ADHD_{MPH-}$ contrast are labeled with capital letters in italics in the 'Cluster description' column. The table is based on Table 5 of reference (140) provided in Supplemental material.

Frequency bin	Comparison	Channels [b]	Cluster size	Cluster description [c]	Scalp topography
$Gamma_1$ [a]	Control vs. $ADHD_{MPH-}$	23	3	C9[.], C10[AFF6h], C14[AF4h] *Cluster A*	Right anterofrontal
	Control vs. $ADHD_{MPH-}$		11	B9[PO10], B10[.], B11[P8], B12[.], B13[P6], B14[TP8], B15[.], B16[CP6], B24[C6], B25[.], B26[T8] *Cluster C*	Right posterior
	Control vs. $ADHD_{MPH-}$		5	B18[CCP4h], B21[.], B22[C4], B30[.], B31[FC4] *Cluster B*	Right central
	Control vs. $ADHD_{MPH+}$	26	19	B3[CPP4h], B4[P4], B6[.], B13[P6], B14[TP8], B15[.], B18[CCP4h], B21[.], B24[C6], B31[FC4] C2[FC2], C4[F4], C11[FFC2h], C12[F2], C13[AFF4h], C21[Fz], C22[.], C23[FCz], C25[F1]	Midline and right frontocentral and right parietotemporal
	$ADHD_{MPH-}$ vs. $ADHD_{MPH+}$	16	12	A2[.], B1[.], C1[FCC2h], C2[FC2], C11[FFC2h], C12[F2], C21[Fz], C22[.], C23[FCz], C24[FFC1h], C25[F1], D1[FCC1h]	Midline and right frontocentral
$Gamma_2$ [a]	Control vs. $ADHD_{MPH-}$	9	3	B12[.], B15[.], B16[CP6] *Cluster D*	Right centroparietal
	Control vs. $ADHD_{MPH+}$	25	16	A2[.], B1[.], B14[TP8], B15[.], B16[CP6], B19[.], B21[.], B22[C4], B23[.], B30[.], B31[FC4], C2[FC2], C3[FFC4h], C11[FFC2h], C12[F2], C22[.]	Right frontocentral
	$ADHD_{MPH-}$ vs. $ADHD_{MPH+}$	8	3	D8[FT7], D22[.], D25[.]	Left frontotemporal

[a] $Gamma_1$: 30-39 Hz, $Gamma_2$: 39-48 Hz

[b] Number of significant channels in the given comparison. (Maximum number of channels is 128.)

[c] BioSemi labels and, where appropriate, International 10-5 System labels between square brackets are listed. Electrode clusters were defined arbitrarily as a group of at least three adjacent scalp derivations with significant group differences in the same direction

3.2.5 Associations of resting-gamma activity and symptom severity

3.2.5.1 Control versus $ADHD_{MPH-}$

We investigated the associations of gamma activity with symptom severity in the three core symptom domains separately, and with their combined score (the total core symptom score) in the electrode clusters with significant group differences. Results are summarized in Table 7.

3.2.5.2 $Gamma_1$ band

There was no significant relationship between $gamma_1$ power and symptom severity in the anterofrontal Cluster A.

Significant negative correlation was found between $gamma_1$ power and total core symptom score (CAARS Core symptom total score: F=8.20, P=0.0052), as well as with the individual core symptom domains (Inattention/memory problems: F=6.81, P=0.0106; Hyperactivity/restlessness: F=7.26, P=0.0084; Impulsivity/Emotional problems: F=4.6, P=0.0347) in the right central Cluster B. Thus, more severe symptoms were associated with lower $gamma_1$ power.

Also, a negative correlation was found between $gamma_1$ power and core symptom total score (CAARS Core symptom total score: F=7.77, P=0.0065) and the three individual core symptom domain scores (Inattention/memory problems: F=4.96, P=0.0284; Hyperactivity/restlessness: F=7.53, P=0.0073; Impulsivity/Emotional problems: F=5.6, P=0.0202) in the extended right posterior Cluster C. Again, more severe ADHD symptoms were associated with lower $gamma_1$ activities.

3.2.5.3 $Gamma_2$ band

There was a significant negative association between $gamma_2$ power with total core symptom score (CAARS Core symptom total score: F=4.79, P=0.0312) and hyperactivity (Hyperactivity/restlessness: F=7.53, P=0.0397) in the right centroparietal Cluster D. Inattention and impulsivity were not statistically significantly related to $gamma_2$ power in Cluster D.

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Table 7

Associations of symptom severity with gamma power by electrode clusters when comparing Control vs. $ADHD_{MPH-}$. Significant correlations are in bold. Cluster B is located right centrally, while Cluster C is an extended posterior right-hemispheric electrode group in the $gamma_1$ threshold. Cluster D is the right centroparietal cluster in the $gamma_2$ frequency range. Results of the anterofrontal Cluster A are not included, as there was no statistically significant finding. Unadjusted p-values listed in this table remain significant after adjusting for multiple testing. Table 7 is based on Table 4 of reference (140).

Covariate [b]	**$Gamma_1$ Cluster B**				**$Gamma_1$ Cluster C**				**$Gamma_2$ Cluster D**			
	μV^2 (SE)		Statistic		μV^2 (SE)		Statistic		μV^2 (SE)		Statistic	
	Low [a]	High [a]	F	p	Low [a]	High [a]	F	p	Low [a]	High [a]	F	p
CAARS core total.	**1.26 (0.15)**	**0.83 (0.09)**	**8.20**	**0.0052**	**1.82 (0.19)**	**1.31 (0.10)**	**7.77**	**0.0065**	**0.91 (0.11)**	**0.67 (0.06)**	**4.61**	**0.0344**
Hyperactivity	**1.18 (0.14)**	**0.46 (0.18)**	**7.26**	**0.0084**	**1.74 (0.17)**	**0.86 (0.22)**	**7.53**	**0.0073**	**0.87 (0.10)**	**0.45 (0.13)**	**4.23**	**0.0427**
Inattention	**1.14 (0.13)**	**0.58 (0.14)**	**6.81**	**0.0106**	**1.65 (0.16)**	**1.07 (0.17)**	**4.96**	**0.0284**	0.84 (0.10)	0.53 (0.10)	3.62	0.0603
Impulsivity	**1.07 (0.12)**	**0.48 (0.21)**	**4.60**	**0.0347**	**1.63 (0.15)**	**0.85 (0.25)**	**5.60**	**0.0202**	0.81 (0.09)	0.47 (0.15)	2.77	0.0996

[a] Least square means estimates (SE) of resting gamma activity for low and high values of the given covariate. Low and high values are 10 and 50 for the total core symptom score and 5 and 30 for the individual core symptom domains.

[b] Covariates:

Conners' Adult ADHD Rating Scale (CAARS) core symptom total score

CAARS Hyperactivity/restlessness factor score

CAARS Inattention/memory problems factor score

CAARS Impulsivity/emotional problems factor score

3.2.5.4 Control versus $ADHD_{MPH+}$

3.2.5.5 $Gamma_1$ band

Significant negative associations were found between $gamma_1$ power and total core symptom severity (CAARS Core symptom total score: F=5.83, P=0.0178), inattention (Inattention/memory problems: F=4.22, P=0.0429), and hyperactivity (Hyperactivity/restlessness: F=6.49, P=0.0125) but not with impulsivity in the frontocentral and parietotemporal clusters while comparing Controls with $ADHD_{MPH+}$. Higher symptom severity was associated with lower $gamma_1$ power.

3.2.5.6 $Gamma_2$ band

Similarly, $gamma_2$ power showed a negative correlation with the total core symptom severity (CAARS Core symptom total score: F=4.04, P=0.0475) and hyperactivity (Hyperactivity/restlessness: F=4.27, P=0.0417) but not with inattention or impulsivity in the right frontocentral cluster in the comparison of controls with $ADHD_{MPH+}$. Higher symptom severity was associated with lower $gamma_2$ power estimations.

3.2.5.7 $ADHD_{MPH-}$ versus $ADHD_{MPH+}$

3.2.5.8 $Gamma_1$ and $gamma_2$ bands

Neither $gamma_1$ nor $gamma_2$ power was significantly related to symptom severity in the identified electrode clusters in the $ADHD_{MPH-}$ vs. $ADHD_{MPH+}$ comparison.

A summary of the results of the correlational analyses is provided in Table 8. Part A reviews results from the Control vs. $ADHD_{MPH+}$ and part B the $ADHD_{MPH-}$ vs. $ADHD_{MPH+}$ comparisons.

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Table 8

Associations of resting-state gamma activity and symptom severity. Significant associations are in bold. The table is based on Table 6 and Table 7 of reference (140) provided as Supplemental material of the article.

Part A: Controls vs. $ADHD_{MPH+}$.

Covariate [b]	**$Gamma_1$ (30-39 Hz)**				**$Gamma_2$ (39-48 Hz)**			
	μV^2 (SE)		Statistic		μV^2 (SE)		Statistic	
	Low [a]	High [a]	F	p	Low [a]	High [a]	F	p
Core total	**1.18 (0.14)**	**0.86 (0.08)**	**5.83**	**0.0178**	**0.76 (0.10)**	**0.36 (0.13)**	**4.04**	**0.0475**
Hyperactivity	**1.15 (0.12)**	**0.55 (0.16)**	**6.49**	**0.0125**	**1.74 (0.17)**	**0.86 (0.22)**	**4.27**	**0.0417**
Inattention	**1.08 (0.11)**	**0.69 (0.13)**	**4.22**	**0.0429**	0.73 (0.09)	0.44 (0.10)	3.85	0.0527
Impulsivity	1.04 (0.11)	0.62 (0.18)	3.03	0.0852	0.67 (0.09)	0.44 (0.15)	1.43	0.2351

Part B: $ADHD_{MPH-}$ vs. $ADHD_{MPH+}$

Covariate [b]	**$Gamma_1$ (30-39 Hz)**				**$Gamma_2$ (39-48 Hz)**			
	μV^2 (SE)		Statistic		μV^2 (SE)		Statistic	
	Low [a]	High [a]	F	p	Low [a]	High [a]	F	p
Core total	0.79 (0.12)	0.62 (0.07)	2.31	0.1324	1.28 (0.21)	1.15 (0.12)	0.37	0.5462
Hyperactivity	0.79 (0.11)	0.44 (0.14)	2.92	0.0909	1.35 (0.19)	0.92 (0.25)	1.31	0.2555
Inattention	0.75 (0.10)	0.51 (0.11)	2.16	0.1456	1.27 (0.18)	1.05 (0.20)	0.56	0.4566
Impulsivity	0.70 (0.09)	0.53 (0.16)	0.61	0.4351	1.13 (0.17)	1.26 (0.28)	0.12	0.7306

[a] Least-squares mean estimates (SE) of resting-state gamma activity for low and high values for a given covariate. Low and high values are 10 and 50 for CAARS core total score, whereas 5 and 30 for the individual symptom domains.

[b] Covariates included the following measures:

Conners' Adult ADHD Rating Scale (CAARS) total core symptom domain score.

CAARS Hyperactivity/Restlessness factor score

CAARS Inattention/Memory problems factor score

CAARS Impulsivity/Emotional problems factor score

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3.3 Results of the second study

3.3.1 Alterations of gamma trajectories in adult ADHD

3.3.1.1 Gamma$_1$ band

The analysis indicated a main effect of group ($F_{(group)}$=11.43, p=0.0009), interactions of linear and quadratic age effect with group ($F_{(linear)}$=19.0, p<0.0001; $F_{(quadratic)}$=16.59, p<0.0001) and MPH treatment status ($F_{(treatment)}$=70.5 p<0001) in the right antero-frontal cluster (Cluster A).

Except for the youngest and oldest ages, significantly lower resting-state gamma$_1$ was found in ADHD than in controls. Treatment with MPH was associated with a 41% relative increase of gamma$_1$ activity in ADHD$_{MPH+}$ in comparison with ADHD$_{MPH-}$.

Trajectories for the patient (ADHD$_{MPH-}$ and ADHD$_{MPH+}$ *combined*) and control groups showed a non-linear developmental path of gamma$_1$ activity. The curves were triphasic: first, gamma$_1$ activity decreased until the middle-ages. This initial reduction was faster in ADHD than in controls. The second phase was a plateau around 40 years, while the third one was an additional increase of gamma power until the late fifties. This increment resulted in higher gamma$_1$ power in the older- than in younger ages, and it was present in the whole sample, in both patients and controls (Figure 5, panel a).

In the right central and extended right posterior clusters (Cluster B and Cluster C) the analysis indicated significant main effects for study group ($F_{(group)}$=15.25, p=0.0001, $F_{(group)}$=43.28, p<0.0001, Cluster B and Cluster C, respectively) as well as interactions for study group with age for both the linear and the quadratic functions ($F_{(linear)}$=16.05, p<0.0001; $F_{(quadratic)}$=6.95, p=0.0087, $F_{(linear)}$=46.84, p<0.0001; $F_{(quadratic)}$=24.09, p<0.0001, for Cluster B and C, respectively]. The main effect of MPH treatment status also obtained significance for both regions ($F_{(treatment)}$=13.12 p=0.0003, $F_{(treatment)}$=127.67 p<0001, Cluster B and Cluster C, respectively).

Except for the youngest ages, gamma$_1$ power was significantly lower in ADHD than in control subjects over time in both scalp regions. Treatment with MPH was associated with a 7% and 26% relative increase of gamma power for Cluster B and C, respectively, in ADHD$_{MPH+}$ relative to ADHD$_{MPH-}$.

Trajectory curves showed that ADHD had slightly higher gamma$_1$ power than controls in the youngest ages (<20 years) in both the right central and right posterior regions (Cluster B and Cluster C, respectively). Then, a curvilinear increase followed in both study groups, with controls exhibiting a faster gamma increase than patients. In the right central region (Cluster B), gamma$_1$ activity reached a plateau during the late thirties-early forties in ADHD, unlike in controls where a similar plateauing was observed slightly later. A curvilinear increase of gamma$_1$ power was found in both study groups over time in the right posterior region, with a plateauing trend more apparent in controls. The last phase of the trajectory curve was a non-linear decrease in both study groups in both regions. Regardless of this decrease, gamma$_1$ power was higher at the upper limits of the investigated age range than in the earliest ages (Figure 5, panels b and c).

Figure 5

Resting gamma$_1$ (30-39 Hz) power trajectory curves in adult ADHD and healthy control groups. Areas in grayscale in the scalp maps embedded in the upper left corners represent the electrode clusters (Cluster A, B, and C) where significant group differences were found in the primary comparison of the first study (Control vs. ADHD$_{MPH-}$).

Red lines illustrate the trajectory curves of ADHD patients, while blue lines illustrate the analogous curves in healthy controls. The filled circles represent the least-squares-mean (LS-mean) estimates of gamma activity at every five years in the age range between 18 and 58 years of age from the ANCOVA model where age was used as a continuous regressor both as a linear and a quadratic function. Shaded bands around the lines represent the 95% confidence limits. Asterisks (*) indicate significant post-hoc comparisons between the patient versus healthy control groups at the given age.

Panel a) demonstrates the gamma$_1$ power trajectories for adult ADHD patients and controls in the anterofrontal electrode cluster (Cluster A). Adult ADHD has a faster reduction of gamma$_1$ power than controls with significantly lower gamma$_1$ power from the mid-twenties to the late fifties. A curvilinear trajectory is seen in both groups.

Panels b) and c) illustrate the trajectory curves for the right central and right posterior electrode clusters (Cluster B and C, respectively). These curves indicate that a non-linear increase of gamma$_1$ power is present both in adult ADHD and in controls in both scalp areas. Adult ADHD patients have a significantly slower increase of gamma$_1$ power magnitude over the entire age range with significantly lower gamma$_1$ power relative to the control group from the mid-twenties. Group differences reach the maximum magnitude at older ages even though a slight decrease of the estimated gamma$_1$ power is to be found by the end of the fifth life decade.

Please find Figure 5 on the next page. This figure is based on Figure 1 of reference (141).

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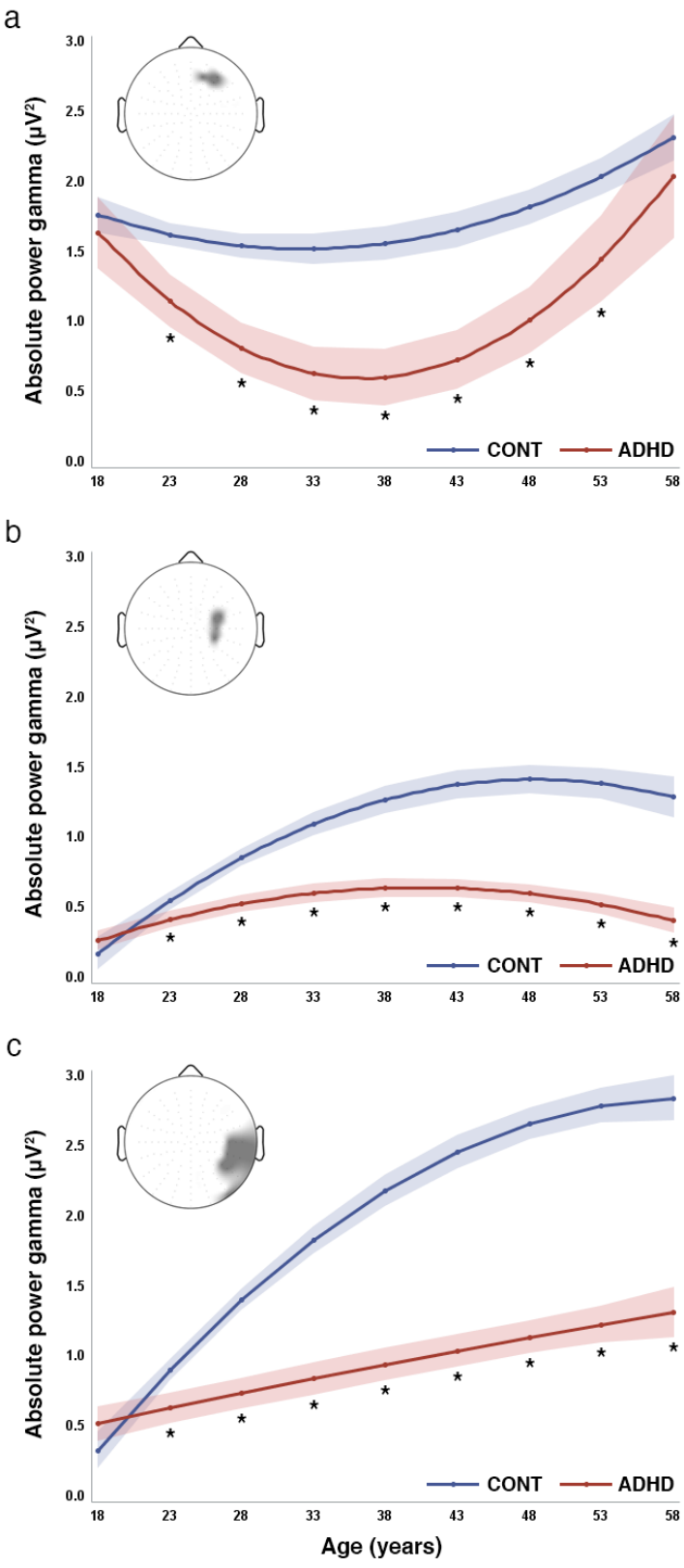

Figure 5

3.3.1.2 Gamma$_2$ band

No significant main effect was found for group ($F_{(group)}$=0.11, p=0.73), or the interaction effect of study group with age concerning the linear ($F_{(linear)}$=1.4, p=0.23) or quadratic functions ($F_{(quadratic)}$=2.29, p=0.13), while MPH treatment status, obtained significance ($F_{(treatment)}$=17.43 p<0001) in the right centroparietal Cluster D.

There were no group differences detected in any age, however controls had numerically higher gamma$_2$ power than ADHD patients except for the upper limits of the age range. $ADHD_{MPH+}$ had an 8% relative increase of gamma activity then $ADHD_{MPH-}$.

Both study groups had a curvilinear reduction of gamma$_2$ power over time with a slight acceleration of the decrease in controls during the mid-fifties. The trajectory exhibited a trend for plateauing in ADHD around the same age.

Figure 6 depicts the trajectory curves for the gamma$_2$ band.

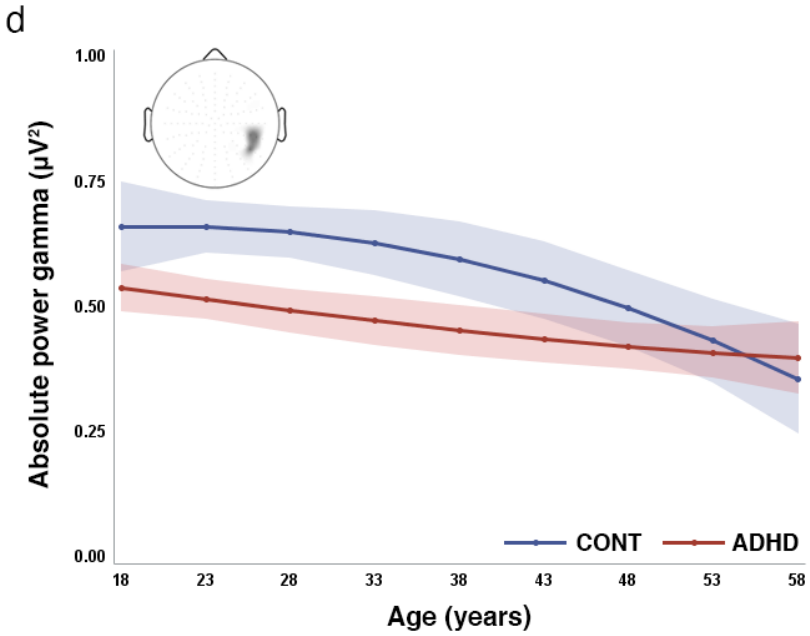

Figure 6

Gamma$_2$ (39-48 Hz) power trajectory curves in the ADHD and healthy control groups. This centroparietal cluster (Cluster D) consists of three electrodes. The scalp map embedded in the graph area represents the scalp location of the electrodes where a significant resting-state gamma$_2$ power decrease was found in the comparison of Controls with ADHD$_{MPH-}$.

The red line represents ADHD patients, while the blue represents healthy controls. Shaded bands represent the 95% confidence limits for each curve. The filled circles represent the least-squares mean (LS-mean) estimates of gamma activity at every five years in the age range from 18 to 58 years. For the computation of the LS-mean estimates and their standard errors, we used the linear and quadratic coefficients of age regressions equations from the ANCOVA model. The interpolation of the trajectory point was based on the regression coefficients from the ANCOVA analysis.

There was a modest, continuous, curvilinear reduction of gamma$_2$ in ADHD with a faster initial part followed by a trend for plateauing. In controls, a slower gamma$_2$ decrease was seen initially, which accelerated in later adult ages. Figure 6 is based on Supplementary Figure S1 of reference (141).

4 Discussion

4.1 Discussion of the first study

The main result of our first investigation (140) was that we identified a significantly lower resting-state gamma frequency band activity in MPH-naïve adult ADHD relative to healthy controls. Scalp localization of the difference was mainly right hemispheric and, to a lesser extent, clustered around the midline. Lower $gamma_1$ activity was associated with more severe ADHD symptoms. A similar negative association was found between $gamma_2$ power and total core symptom severity and hyperactivity.

4.1.1 Comparison of the results with childhood ADHD findings

To our knowledge, diminished resting EEG gamma power has not been reported previously in adult ADHD. However, prior publications observed lower gamma activity in children with ADHD in comparison with healthy peers, which is consistent with our findings. For example, Barry et al. (104) found diminished left posterior activity (defined as the average power in T5, P3, and O1 channels), and in another study (103), bilateral gamma power decrease in childhood ADHD versus controls. Dupuy et al. (75) reported lower global and posterior gamma activity in girls with ADHD. It is also to note that weaker resting and stimulus-induced gamma-band activity was also observed in MEG studies by Wilson et al. (105, 142, 143).

4.1.2 The potential links between the resting-state and task-positive gamma findings in ADHD

We found a predominantly right centroparietal and posterior gamma power decrease in ADHD irrespective of medication status since both the MPH-treated and MPH-naïve ADHD groups exhibited it (was found in both the Control vs. $ADHD_{MPH-}$ and Control vs. $ADHD_{MPH+}$ comparisons).

Since gamma activity is typically investigated under task conditions (while performing perceptual, attentional, or higher-order cognitive tasks), most of our knowledge pertains to event-related, stimulus-locked gamma oscillations. Therefore, the intrinsic activity of the neural networks (without the performance of a goal-directed task) necessitates further investigations. Perception, execution of attentional- and/or working memory tasks

increases gamma-band oscillatory activity relative to the pre-stimulus baseline in healthy persons (144-147). Our diminished $gamma_1$ and $gamma_2$ activity results are at least partially at variance with previous literature on stimulus-locked gamma oscillations in childhood ADHD, although this literature seems somewhat controversial. Specifically, Lenz et al. (148) reported increased evoked gamma response in the early visual perception of ADHD children relative to healthy peers in a target recognition task. Similarly, higher oscillatory gamma responses were observed in the centroparietal electrodes (C3, P3) during an auditory selective attention test (100) and occipitally in a working memory test with distractors in children with ADHD when compared to healthy controls (149).By contrast, diminished gamma responses were reported in childhood ADHD versus controls while performing a force choice-reaction test, which demanded the shift of attention (150) or in MEG studies on adults during a time estimation task (105) and during passive auditory stimulation (143).

4.1.3 Decreased resting gamma power and cortical hypo-arousal in adult ADHD

According to the extended hypo-arousal model of ADHD (74, 76, 151, 152), the pathophysiology of the disorder is possibly attributable to an abnormal synergy between the tonic and phasic firing of the norepinephric locus coeruleus neurons, which leads to suboptimal cortical arousal and less effective enhancement of the signal-to-noise ratio in the presence of stimulation or under task-conditions in general (153). In light of this, it is conceivable that our finding of diminished centroparietal gamma power represents an under-aroused cortical state. In contrast, the augmented evoked gamma responses roughly at the same scalp areas published by previous literature represent compensatory mechanisms to enhance the signal-to-noise ratio and thereby assist the orientation and sustainment of attention in ADHD. Central and peripheral electrophysiological correlates of under-arousal include higher theta power, lower power in higher frequency bands (61, 65, 154, 155), higher theta/beta ratio (58, 65, 154, 155), decreased skin conductance level (155-158), diminished P3 (159-162) and contingent negative variation (CNV) amplitude (158, 163, 164). To our knowledge, only one previous publication (75) reported both decreased EEG gamma power and lower skin conductance (central and peripheral arousal) in an ADHD sample. Gamma power and skin conductance level also showed a significant association, which may reflect a link between gamma activity and under-

aroused conditions. Although we did not investigate peripheral arousal directly, the above results can be viewed as a support for the assumption that lower gamma power is a hallmark of central hypo-arousal and thereby these results can be interpreted in the context of the hypo-arousal model of ADHD.

4.1.4 The associations of decreased gamma power and symptom severity

We also found a negative association between spontaneous gamma activity and symptom severity, including inattention. As gamma activity is considered a hallmark of network functioning (87, 88), such a relationship might reflect a regulation abnormality of the intrinsic neural networks involved in the organization of attentional capacity. According to the network dysregulation theory, which assumes an imbalance of interrelated neural network functioning and cognitive processes, abnormal brain organization can contribute to the pathophysiology of ADHD (165-169). ADHD is characterized by the inability to discriminate between relevant and irrelevant stimuli, focus and sustain attention, and control (inadequate) behavioral responses. These disturbances might be attributable to an imbalance between the default mode network (DMN) and the salience network (SN), and the dorsal and ventral attentional networks (DAN and VAN, respectively). Previous functional connectivity studies demonstrated that the DAN and the VAN are functionally less segregated in ADHD, leading to attentional deficits. Besides, there is an imbalance between the salience and dorsal and ventral attention networks, resulting in a worse functional filtering performance in ADHD (166). The difficulty of switching from rest to task-positive conditions has also been reported in ADHD and was attributed to a functional imbalance between the default mode network and task-positive networks (165, 170, 171). Thus, our finding of decreased spontaneous gamma activity might reflect a dysfunction in the coupling between resting-state neural networks or an abnormality in the capacity of the switching process (from default to task-based conditions), which might contribute to the significant associations between gamma activity and symptom severity in our study.

4.1.5 Scalp topography of the group differences

We also found that gamma activity reduction exhibited a right-lateralized topographic distribution. According to the modified attentional model of Corbetta et al. (137, 172),

the dorsal and ventral attentional networks are functionally segregated but have a mutual influence on each other's operation. Visual spatial attention is right-lateralized mainly due to the asymmetries of the ventral attentional network. The main support of this hypothesis is the contralateral spatial neglect found in stroke patients with right hemispheric lesions (173). Another hallmark of the lateralization of the VAN is the well-documented left-biased behavior (pseudoneglect) in healthy persons during spatial attention tasks (174, 175). The electrophysiological background of this biased behavior is also delineated in the literature as an asymmetry of the visual ERP component N1, which corresponds with the early phase of visual information processing and peaks at the electrode PO4, localized close to the temporoparietal junction (176).

The temporoparietal junction is engaged in the functioning of the VAN and the DMN. Right lateralized spatial attentional deficit (a neglect-like deficit or pseudoneglect in spatial attention) measured by an asymmetry index (ratio of left and right hemifield distractor effects) has already been reported in adult ADHD. The deficit found in ADHD was milder in severity but the same in quality as in patients with right hemispheric parietal damage with neglect and differed significantly from healthy persons or patients with right hemispheric damage without neglect (177). The involvement of the right hemisphere in the pathophysiology of ADHD is further supported by the data from prior structural (178-182) and functional (183) imaging studies.

With respect to our results, we assume an imbalance between the right-lateralized VAN and the functionally symmetrical DAN, which might have been present during our task-free EEG recording off-task but with a sustained, permanent visual input (as the eyes were open during the recording). This imbalance might have been reflected in the decreased gamma power in both gamma ranges. Lower spontaneous gamma activity may represent cortical dysfunction which can be present due to a reduced capacity to maintain attention by the DAN and/or lower capacity to filter irrelevant stimuli by the VAN, thereby interfering with normal DAN function in ADHD (166). The right dominance of spontaneous gamma power decrease may occur due to deficits of visuospatial attention caused by a functionally asymmetric VAN (137, 172, 184) and its stronger functional connections with the DAN in ADHD compared with healthy persons (166). Although the above-discussed functional deficit in relation to the attentional networks was visual pseudoneglect, it is important to underline that the synchronized operation of the VAN

and the DAN is not restricted to the visual modality and spatial and non-spatial deficits are often associated. Abnormal functionality in our study sample was represented by the high CAARS total score and core symptom scores, which capture clinically relevant symptoms of attentional dysfunctions in ADHD.

4.1.6 Gamma band differences between the ADHD subgroups

Although the comparison of the $ADHD_{MPH-}$ with the $ADHD_{MPH+}$ group was out of the focus of our study, it is worth noting that $ADHD_{MPH+}$ had significantly lower gamma power than $ADHD_{MPH-}$. According to the relevant literature, stimulant medication has a normalizing modulatory effect on EEG measures, including gamma power. Previous investigations utilizing MEG found that acute post-medication gamma activity increases over several brain areas during task performance relative to the pre-medication baseline (105, 143, 185), and measures of post-treatment functional connectivity also approximated the levels found in healthy persons (186). These changes in functional connectivity were observed in, but not limited to, brain areas in correspondence with the default mode network (187). Thus, regarding our seemingly counterintuitive results of lower spontaneous gamma power in $ADHD_{MPH+}$, we should consider that 1) patients in the $ADHD_{MPH+}$ subgroup were on chronic stimulant treatment, and 2) pre-treatment values of gamma power were not available. Patients in the $ADHD_{MPH+}$ subgroup had been referred to pharmacologic treatment at relatively young ages, which is reflected in their substantially (but not statistically) lower mean age relative to $ADHD_{MPH-}$. Therefore, this subgroup may represent a clinically more severe manifestation of ADHD pathology, which might have co-occurred with an even more pronounced pre-treatment gamma reduction. In light of the above, we think that our results do not directly contradict previous findings reporting the normalizing effect of stimulant medication on EEG measures. Nonetheless, further studies are needed to investigate treatment response in the $ADHD_{MPH+}$ sample.

4.1.7 Limitations of the first study

There were several limitations of our first study. First, although high-density EEG recording systems provide excellent two-dimensional topographical resolution, their information on the brain sources of scalp-recorded bioelectric signs is limited. Second, as

EEG was recorded only eyes-open, we could not compare spontaneous gamma activity with and without sustained visual stimuli. Thus, additional studies are needed to further explore gamma alterations in task-negative (eyes-open and eyes-closed) and task-positive situations with and without the presence of stimulant medications. Nonetheless, despite the limitations, reduced centroparietal gamma power might reflect an abnormal intrinsic visual spatial attention network in adult ADHD, which needs further investigations.

4.2 Discussion of the second study

The main finding of our second study (141) is a different developmental trajectory of resting EEG gamma$_1$ (30–39 Hz) but not gamma$_2$ (39-48 Hz) power in adult ADHD in comparison with healthy controls. To our knowledge, our second study is the first to explore the changes in resting EEG gamma power with age in adult ADHD. Despite that ADHD is considered a lifelong neurodevelopmental disorder, the potentially altered adult course of its electrophysiological correlates, including spontaneous gamma power, remains poorly addressed.

4.2.1 Gamma-band trajectory curves in adult ADHD and controls

The trajectory curves in both groups 1) exhibited a tri-phasic, non-linear appearance, 2) depicted a gamma$_1$ power increase over time, and 3) were different from each other in the anterofrontal than in more posterior (right central and right posterior) locations.

In the anterofrontal areas (Figure 5, panel a), patients with ADHD had a faster decline of gamma$_1$ power than controls (phase 1), followed by a plateauing trend (phase 2) and a late re-increase (phase 3), leading to higher observed power values at the upper limits of the age range than in the lower end. Except for the estimations for youngest and oldest ages, ADHD patients had significantly lower gamma$_1$ power than healthy controls at all ages. In the right central and right posterior scalp regions, however, (Figure 5, panels b and c, respectively), both ADHD and controls had a non-linear increase of gamma$_1$ power over time, resulting in higher gamma$_1$ power at older than in younger ages. At first, an increase was seen (phase 1), which was remarkably slower in patients than in controls. This increase was followed by a trend for plateauing in the middle-ages (phase 2) and then a slight diminution in both groups at the older age ranges (phase 3). Visual inspection of the curves indicates that the plateauing tendency occurred slightly earlier (around 43

years of age vs. 48 years) in the central region than in the posterior one. Except for the youngest ages (<20 years of age), ADHD patients had significantly lower $gamma_1$ power at all ages than controls. Interestingly, ADHD patients had slightly but not statistically higher $gamma_1$ power than controls in the youngest ages (<20 years of age) right centrally and in the right posterior regions.

We also note that both groups' $gamma_2$ power decreased over time without significant group- or group-by-age interaction effects.

As it has already been discussed in the previous sections of this thesis, decreased EEG gamma activity in childhood- (75, 103, 104) and weaker MEG gamma activity in adult ADHD (105, 143) has already been reported in the previous literature as an overall group effect. Measurement data has been averaged from subjects of the age ranges 7-12 years in the case of the childhood studies and 30-58 years in adult MEG studies. The analyses performed in these experiments did not include age or group-by-age interaction effects. It should also be kept in mind that data on gamma activity in childhood ADHD derives from patient samples at a relatively young age, and it is still unclear whether, and how this difference changes from childhood to adolescence and later to early adulthood. The MEG results of the Wilson group (143) and the findings of our first study suggest that gamma activity is also diminished in adult ADHD in samples with mean ages in the middle-aged range (41.8 and 30.9 years in case of the Wilson group and our results, respectively). However, we think that further studies should precisely aim the transition period to and from adolescence to decide whether the observed gamma decrement is subject to marked developmental changes.

4.2.2 Alterations of the EEG development in ADHD in the traditional frequency bands (< 30 Hz)

Previous publications investigating different age cohorts with and without ADHD in the classical EEG bands (<30 Hz) typically report a strong effect of age in terms of decrease in power measures from delta to beta frequency bands over time both in patients and controls (60, 135). In a longitudinal follow-up study of childhood ADHD subjects with an average follow-up time of 11 years by Clarke et al. (134), the authors found significant decreases in relative theta and delta band power, accompanied by an increase of relative alpha and beta band power in persistent ADHD cases relative to their childhood baseline.

Absolute power measures were not reported in this work. The only positive finding regarding altered developmental trajectories in the classical frequency bands has been published by Poil et al. (68), who found that beta power decreased from childhood to adult ages in both patients and controls. However, ADHD patients exhibited only a smaller, localized frontocentral and occipital reduction in power, unlike controls, where the diminution was global. The authors report a non-significant numerical reduction with age in the whole study sample regarding gamma power. We can conclude that previous literature shows that the electrophysiological maturation from child- to adulthood in the classical EEG bands in ADHD is fairly similar to that in controls, with strong age- but very limited age-by-group interaction effects. These results may not be able to lead to significant changes in ADHD diagnostics as machine-learning-based diagnostic approaches based on EEG measures only classify age with high accuracy, but their sensitivity to classifying ADHD status is limited (68, 135).

Our results show that the adult developmental trajectories of resting $gamma_1$ power exhibit significantly lower power in ADHD than in healthy controls across almost the entire age range we examined. Although our study did not investigate the cortical structure, we propose that this decrease may be related to the abnormal cortical development previously reported in ADHD samples (180, 188), as gamma-band EEG activity is mainly generated by cortical neurons. Nonetheless, due to the scarce data on the normal adult developmental course of spontaneous gamma power and its possible abnormalities in mental disorders, it would be premature to conclude that our findings are reflections of structural neurodevelopmental deviations and are specific to ADHD.

4.2.3 Comparison with the gamma-band trajectories in healthy persons

As mentioned before, data on age-related changes of resting gamma power is scarce. We could identify only one paper (189) that addressed the question directly. Tierney et al. reported a linear decrease of log-transformed global (averaged gamma-band activity across all the 19 scalp channels) gamma power (31-50 Hz) in a healthy cohort aged 3–38 years. However, it is of note that we investigated a broader age range (18-58 years of age). Therefore, we could delineate the course of gamma activity in older ages. Furthermore, by utilizing a high-density recording system and a channel-wise analysis, we were also able to identify specific scalp regions representing prominent areas affected

by gamma decrease, and thereby we could detect different trajectory curves in the anterofrontal cluster than elsewhere. Our results are partially in line with Tierney et al., in that anterofrontal gamma power trajectories exhibited a decrease of gamma activity in the initial part of the curves (phase 1) in both study groups. However, our findings suggest a topographic specificity of gamma-band power trajectories rather than a global effect.

4.2.4 Regional differences of gamma-band trajectories

Regarding scalp topography, our results indicate that the developmental path of gamma power in adults in the anterofrontal region differs from those found in the right central and right posterior regions. Normal CNS maturation follows a topographical order with respect to neuroanatomy and electrophysiology from child- to early adulthood. Moreover, MRI and EEG findings highly correlate with each other (133). Structural MRI studies show a marked decrease following the non-linear increase of gray matter volume from childhood to adolescence during and even after puberty due to synaptic pruning. This process substantially accelerates until around the thirties (190), but there is a lack of data regarding older ages. Regarding topography, prior MRI data shows that the convexities' maturational process starts around the central sulcus, and in the frontal cortex, it progresses rostrally from the sensorimotor cortex reaching the dorsolateral prefrontal cortex at the latest. The parietal lobe matures earlier than the frontal lobe, and the GM volume reduction begins in the postcentral sulcus and progresses laterally. The frontal, occipital and temporal poles mature early. The temporal lobe exhibits a relative late maturational pattern, and the angular gyrus develops the latest. On the inferior surface of the brain, however, most structures in the frontal and temporal lobes mature early except for the orbitofrontal cortex (191, 192).

A topographically specific developmental pattern has also been delineated in electrophysiological signals, but it is also to note that sub-beta frequencies have different developmental topographies as beta rhythm. As the consequence of synaptic pruning, a non-linear decrease in total- and absolute power is observed over time (132) as the EEG signals are mainly, but not exclusively attributed to the rhythmic operation of cortical pyramidal cells (133). In the case of sub-beta bands, this maturation begins occipitally and progresses rostrally. In the case of the beta bands, however, the starting point is located around the Cz and then propagates to the caudal (Pz) and later lateral directions

and affects the frontal channels the latest (132). There is also a debate on how beta band power changes over time: The classical theory is that beta power decreases with the other bands over time (129). But, as it is generated by less synchronized cortical neurons (therefore the low voltage/power data), it is possible that pruning induces an increase, not a diminution of absolute beta as the consequence of a relative increase in synchronization with the decrease of synapses with the pruning process (133).

In the interpretation of our results, we should also consider that our study sample is composed of adults from 18 to 58 years of age. The investigation of such a broad age cohort has rarely been performed in the ADHD literature so far. As middle-aged and older individuals have also been enrolled in our study, the early signs of age-related normal cortical thinning might also affect our findings. It has already been demonstrated that even healthy, middle-aged individuals exhibit cortical thinning in the prefrontal, frontal, and, to a lesser extent, in the parietal heteromodal association cortices (193, 194). As we discussed above, these cortical areas develop relatively late or the latest but also deteriorate the earliest during the lifespan ("last-in, first-out principle" (194, 195)). The role of the "last-in, first-out" hypothesis has also been proposed in case of P300 developmental trajectories in adult ADHD (196). Similar to the development, age-related reductions of the cortical structure and subcortical gray matter show regional variations in extent and speed (197-200). Our results about the different trajectories seen in the anterofrontal than in more posterior leads might reflect these differences in development (and deterioration). Nonetheless, it should be pointed out that scalp-recorded EEG is not exclusively produced by the cerebral cortex but is the summation of all signals generated by cortical and subcortical sources.

ADHD is more recently explained in the context of the network dysfunction hypothesis [164]. As we already mentioned in previous sections of this thesis, spontaneous EEG band power, and resting-state cortical networks are intercorrelated (115, 201, 202). Specifically, gamma-band activity is associated with the synchronized operation of task-positive and resting-state networks (171). Our results that show different resting $gamma_1$ trajectories in patients than in controls might reflect altered network operations observable throughout the entire lifespan and thereby underline the disorder's lifelong nature.

4.2.5 The effect of methylphenidate to gamma-band trajectories

Our analysis revealed that MPH treatment status had a significant main effect and resulted in a relative increase of gamma activity with various extent in the different regions in the MPH-treated, relative to the untreated group. This growth is consistent with data from previous studies indicating an increase of gamma-band measures with stimulant treatment, even though not MPH specifically. The acute administration of dexamphetamine induced the increase of resting gamma power (30-45 Hz) (203), 40 Hz auditory steady-state response (204), and early post-stimulus (50 ms) gamma-range activity during an auditory oddball task (205) in healthy volunteers compared to their off-medication baseline. Similar findings have been reported in points of spontaneous gamma-range (30-106 Hz) MEG activity (105) and 40 Hz auditory steady-state response (143) elicited by the administration of mixed amphetamine salts in adult ADHD patients. However, it is important to underline that, as our study had a cross-sectional design, no direct causal relationship with treatment can be declared.

4.2.6 Limitations of the second study

There are also several limitations of our second study. First, we applied a cross-sectional study design to delineate the relationships of gamma power with age. Due to feasibility reasons, cross-sectional designs are commonly used in studies aiming to describe age-related changes in imaging studies. Nonetheless, longitudinal studies would be important to confirm our results. Second, the age distribution of our study groups was not uniform across the investigated age ranges. This condition typically occurs in cross-sectional studies examining different age cohorts. At the same time, no significant differences between the proportions of lower- (< 25 years), middle- (25-35 years), and higher-aged (> 35 years) subjects have been found. Nonetheless, we think that future studies should use a more targeted sampling design to ensure a uniform age distribution. Third, our study focused exclusively on adults. Therefore, it was not possible to draw conclusions about the developmental path of gamma activity in the youngest age range (<20 years), where partially different trends emerged than in other age groups and where even more significant age-related changes are expected given that this age represents the transition period of CNS development from adolescence to early adulthood. Fourth, since our study sample consisted of either clinically diagnosed ADHD or healthy subjects, our findings

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are limited only to those who fulfill disease criteria as adults. As 40-60% of childhood ADHD cases totally or partially remit until adulthood, further studies are needed to investigate gamma power trajectories in remitters and/or relatives of ADHD probands to delineate the course of development in the broader phenotype.

5 Conclusions

5.1 Conclusions of the first study

The main finding of our work indicates lower task-free, spontaneous $gamma_1$ (30-39 Hz) and $gamma_2$ (39-48 Hz) band power in adult ADHD patients relative to matched controls with eyes-open. Gamma band power in both frequency ranges was lower in medication-naïve cases and patients on long-term MPH treatment ($ADHD_{MPH-}$ and $ADHD_{MPH+}$, respectively) than in controls. Topographical distribution of group differences clustered in the right centroparietal scalp areas in both investigated gamma frequencies. Spontaneous gamma power exhibited a significant inverse association with ADHD symptom severity. The widely cited hypo-arousal model of ADHD offers a plausible interpretation of our results. On the other hand, gamma power is associated with cortical network functioning, and the two-dimensional scalp distribution of the gamma activity reduction in adult ADHD was mainly right hemispheric and exhibited partial overlap with the approximate cortical localization of the dorsal attention network. Therefore, we propose that our results should rather be interpreted in the context of the more recent network dysfunction hypothesis. In the light of the negative associations of gamma power and symptom severity, our results may indicate a right centroparietal cortical dysfunction caused by the decreased activity of the dorsal attention network or an imbalance between the functionally lateralized ventral- and non-lateralized dorsal attention networks. Although additional research is needed to further explore our results, we believe that our novel findings provide an important addition to the field of electrophysiological biomarker research in adult ADHD.

5.2 Conclusions of the second study

The main finding of our second study is that a curvilinear/non-linear association between resting $gamma_1$ power (30-39 Hz) exists in patients with adult ADHD. Resting $gamma_1$ power increased over time both in patients and controls. The resting gamma-band power trajectory curves are similar in patients and controls and exhibit a triphasic appearance. ADHD patients had significantly lower $gamma_1$ power than controls across most parts of the investigated age range (18-58 years) in our sample. The maximum group difference in the anterofrontal region was found around the age of 40 years, and thereafter the

difference decreased in older ages. In the right central and right posterior regions, however, differences in $gamma_1$ power increased over time. Our findings suggest that lower resting $gamma_1$ activity is stable over time in adult ADHD. Besides, developmental paths of spontaneous gamma power might be different in the anterior regions than in central and posterior locations. We propose that the results can be interpreted within the context of the dysfunctional network hypothesis and that they might reflect deviations of the cortical organization relative to controls. As ADHD is a neurodevelopmental and lifelong disorder, these deviations possibly reflect structural alterations and an abnormality in network dynamics during the late phase of central nervous system development and early aging in ADHD. Apart from their novelty, the importance of our exploratory findings is that they underline the lifelong nature of ADHD and possibly might help to gain further insight into the age-related changes of potential electrophysiological biomarker candidates for use in the clinical setting.

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6 Summary

Objectives: The first study aimed to delineate resting EEG gamma-band power in patients with adult ADHD and to investigate its associations with symptom severity. Moreover, it aimed to characterize the topography of the group differences. The goal in the second study was to delineate resting EEG gamma-band trajectories in adulthood.

Methods: 101 subjects were enrolled (42 adult ADHD patients, 59 healthy controls). To investigate group differences, patients were stratified according to methylphenidate status (25 $ADHD_{MPH-}$, 17 $ADHD_{MPH+}$). Spatial repeated measures ANCOVA was used to investigate group differences of resting gamma-band power. Statistical analysis based on mixed model approach was used to estimate the associations of gamma power and symptom severity in the whole study sample. To capture topographical differences, electrode clusters were defined as an aggregate of at least three EEG channels with significant group differences in the same direction. To delineate gamma trajectories, ANCOVA was used, in which age served as a continuous regressor defined as linear and quadratic functions.

Results: Resting gamma power was significantly decreased in ADHD compared to controls, regardless of medication status. Gamma power was negatively correlated with symptom severity. The topographical distribution of the group differences was mainly right hemispheric, central- and posterior. ADHD patients had different developmental paths than controls, with generally lower gamma power across all ages. The course of the trajectories in anterior electrodes differed from those in central and posterior locations.

Discussion: The decreased gamma power in adult ADHD is consistent with data from ADHD children. Our results can indicate network dysfunctions or imbalances of resting-state networks in ADHD, which was captured by the association of lower gamma power with symptom severity in the study sample. The topographic distribution of the differences might derive from the imbalance of the lateralized attentional networks. To our knowledge, we were the first to report resting EEG gamma-band trajectories in adult ADHD. Non-linear trajectory curves were found in both groups. The course of the trajectories in ADHD differed from those found in controls. Gamma-power increased with age. The different course of anterofrontal trajectories relative to posterior ones is interpreted in the context of the "last in, first out" hypothesis, which assumes that brain maturation and deterioration follow opposite spatial patterns over time.

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8 Bibliography of the candidate's publications related to the thesis

1. Tombor L, Kakuszi B, Papp S, Réthelyi J, Bitter I, Czobor P. (2021) Atypical resting-state gamma band trajectory in adult attention deficit/hyperactivity disorder. J Neural Transm (Vienna), 128(8): 1239-1248.

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9 Bibliography of the candidate's publications not related to the thesis

1. Becske M, Marosi C, Molnár H, Fodor Z, Tombor L, Csukly G. (2022) Distractor filtering and its electrophysiological correlates in schizophrenia. Clin Neurophysiol, 133: 71-82.

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