Reduced fronto-cortical brain connectivity during NREM sleep in Asperger syndrome: An EEG spectral and phase coherence study

Alpár Sándor Lázár [a,*], Zsolt Iosif Lázár [b], Andrea Bíró [c], Miklós Győri [d], Zsanett Tárnok [c], Csilla Prekop [c], András Keszei [a], Krisztina Stefanik [d], Júlia Gádoros [c], Péter Halász [c], Róbert Bódizs [a]

[a] *Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary*
[b] *Faculty of Physics, Babeș-Bolyai University, Cluj-Napoca, Romania*
[c] *Vadaskert Child Psychiatric Hospital, Budapest, Hungary*
[d] *Autism Foundation and Research Group, Budapest, Hungary*

ABSTRACT

Objective: To investigate whether sleep macrostructure and EEG power spectral density and coherence during NREM sleep are different in Asperger syndrome (AS) compared to typically developing children and adolescents.
Methods: Standard all night EEG sleep parameters were obtained from 18 un-medicated subjects with AS and 14 controls (age range: 7.5–21.5 years) after one adaptation night. Spectral, and phase coherence measures were computed for multiple frequency bands during NREM sleep.
Results: Sleep latency and wake after sleep onset were increased in AS. Absolute power spectrum density (PSD) was significantly reduced in AS in the alpha, sigma, beta and gamma bands and in all 10 EEG derivations. Relative PSD showed a significant increase in delta and a decrease in the sigma band for frontal, and in beta for centro-temporal derivations. Intrahemispheric coherence measures were markedly lower in AS in the frontal areas, and the right hemisphere over all EEG channels. The most prominent reduction in intrahemispheric coherence was observed over the fronto-central areas in delta, theta, alpha and sigma EEG frequency bands.
Conclusion: EEG power spectra and coherence during NREM sleep, in particular in fronto-cortical derivations are different in AS compared to typically developing children and adolescents.
Significance: Quantitative analysis of the EEG during NREM sleep supports the hypothesis of frontal dysfunction in AS.

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1. Introduction

Sleep holds promise as a sensitive indicator of changes in brain neuronal organization in a large number of conditions, including psychiatric (Leistedt et al., 2009) and neurodevelopmental disorders (Lázár and Bódizs, 2008).

Asperger syndrome (AS) is a neurodevelopmental disorder characterised by impairment in social interactions, manifest repetitive and stereotyped behaviours and interests without significant delay in language or cognitive development (APA, 2000). Genetic, neurophysiologic, cognitive and behavioural data support the hypothesis that AS is a variant of autism located at the milder end of the spectrum of autistic disorders (Frith, 2004). This may imply that neurobiological findings for high functioning autistic patients can in part be generalized to AS.

Assessments of brain development based on measurement of head circumference, magnetic resonance imaging and post-mortem brain weight revealed that autism is characterised by a period of unusually rapid rate of early brain growth followed by abnormally slow or arrested growth (Redcay and Courchesne, 2005). It has been proposed that this early overgrowth interferes with the normal developmental trajectory of connectivity in the cortex (Courchesne and Pierce, 2005). Post-mortem neuropathologic studies of autistic brain have shown various abnormalities (Bailey et al., 1998; Casanova et al., 2002). These abnormalities include changes in the cortical microanatomy, mainly in frontal areas and this may provide evidence for cellular abnormalities and processes that may underlie the brain growth abnormalities which primarily affect the frontal lobe (Carper and Courchesne, 2005; Herbert et al., 2004).

It has been hypothesized that these altered patterns of brain neural development result in a local overconnectivity in the frontal

cortex and a reduction in long-distance cortical–cortical coupling (Courchesne and Pierce, 2005). The frontal overconnectivity and the long-distance underconnectivity are thought to underlie the cognitive characteristics of autism spectrum disorders (ASD).

In accordance with these studies, functional imaging assessments showed that in autistic subjects brain activity was less synchronized across activated brain areas during a variety of cognitive tasks, including sentence comprehension (Just et al., 2004), executive functions (Just et al., 2007; Koshino et al., 2008), visuo-motor performance (Villalobos et al., 2005), social cognition (Castelli et al., 2002; Kana et al., 2008) and also during the baseline resting-state (Cherkassky et al., 2006). These findings imply that impairments in cognitive domains such as executive function (Hill and Bird, 2006), complex information processing (Minshew et al., 2002), theory of mind (Baron-Cohen et al., 1985) and empathy (Baron-Cohen, 2002) may all be related to abnormalities in neocortical connectivity in ASD.

EEG studies and analyses of the EEG during NREM in particular may provide further insight into functional brain connectivity (Miyamoto et al., 2003) also in ASD (Rippon et al., 2007); Several relevant EEG measures are available. An EEG spectral profile in NREM sleep is characteristic for an individual, possibly, reflecting individual traits of functional neuroanatomy (Finelli et al., 2001; De Gennaro et al., 2008). Developmental features and functional as well as structural characteristics of cortico-cortical and thalamo-cortical networks are likely to have a general effect upon a large range of EEG frequencies. The various frequencies in the EEG reflect different neural sources that subserve different brain functions (Buzsáki and Draguhn, 2004) and studying EEG spectra topographically and over a large range of frequencies may provide information about the underlying neurophysiological systems. Slow waves and sleep spindles are key EEG characteristics of NREM sleep and are functionally dependent on the thalamo-cortical network (Steriade, 2006), a system shown to be modified in autism (Tsatsanis et al., 2003; Hardan et al., 2006). These EEG activities have been shown to be affected in small groups of AS subjects (Godbout et al., 2000; Limoges et al., 2005). However, there are currently no data of spectral measures involving a broad range frequency bands and topographic patterns in subjects with ASD.

An EEG measure particularly sensitive to changes in connectivity is EEG coherence. Based on the principle 'What is wired together, fires together' it is assumed that EEG phase coherence indices, which are primarily measures of phase correlation, reflect synchronous co-activation of different brain areas (see a review in Sauseng and Klimesch, 2008).

Studies in control subjects have shown that both intrahemispheric and interhemispheric coherence of EEG activity reaches a high level in NREM sleep primarily in low delta frequency band (1–2 Hz) and is largely independent of the signal amplitude (Achermann and Borbély, 1998a) reflecting large-scale functional connectivity of brain regions (Achermann and Borbély, 1998b). NREM sleep specific inter- and intrahemispheric EEG coherence is enhanced by learning reflecting possible reactivation of learning induced brain connections (Mölle et al., 2004). Sleep coherence measures may be relevant for understanding the abnormal functional neuroarchitecture assumed to underline the particular behavioural and cognitive phenotype in ASD. It is important to mention that the neuroarchitectural substrate of the two types of coherences is different. The transcallosal fibres contribute to interhemispheric coherence while other types of fibres, including subcortical–cortical and cortico-cortical fibers, contribute to intrahemispheric coherence (Nielsen et al., 1993).

Some of the previous PSG sleep studies in subjects with high functioning autism (HFA) and AS reported alterations in sleep macrostructure such as longer sleep latency, more frequent nocturnal awakenings, lower sleep efficiency, increased duration of stage 1

sleep, and decreased slow-wave sleep (Godbout et al., 2000; Limoges et al., 2005). The results of other studies, however, are not consistent with these results (Bruni et al., 2007; Malow et al., 2006; Miano et al., 2007; Tani et al., 2004). This may be due to methodological issues related to the subjects' age range, distinct subtypes of ASD or co-morbid mental retardation. More detailed analyses of NREM EEG identified a decreased number a visually detected sleep spindles (Godbout et al., 2000; Limoges et al., 2005), a non-significant decrease in delta and increase in theta power (Tani et al., 2004), and a significant increase (Bruni et al., 2007) of A1 type Cyclic Alternating Pattern, which supposedly reflects an altered thalamo-cortical and cortico-cortical connectivity pattern, in subject with AS and HFA (Bruni et al., 2007).

The current study was designed to extend previous sleep research in AS. Sleep macrostructure was analyzed to further explore PSG determined sleep patterns in AS, and to better understand the basis of the frequent sleep complaints in this population in this vulnerable period from childhood to late adolescence. The regional distribution of spectral activity across a wide range of frequency bands, and of inter- and intrahemispheric coherence was analyzed to gain a better insight into the functional brain architecture underpinning the peculiar cognitive, affective and behavioural phenotype in AS.

Based on the hypothesized changes of the thalamo-cortical system in ASD (Tsatsanis et al., 2003; Hardan et al., 2006; Limoges et al., 2005) we predicted an altered NREM sleep EEG spectral profile across a large range of frequencies in children and adolescents with AS.

Based on the neurobiological, neuropsychological, functional imaging data and on the long-distance underconnectivity hypothesis of the frontal region with other brain areas (Courchesne and Pierce, 2005; Just et al., 2004) in subjects with ASD we predicted a decreased inter- and intrahemispheric coherence of NREM EEG between the frontal region and other cortical areas in AS. Local overconnectivity could not be assessed by coherence analyses, because this requires high density EEG recordings (Grieve et al., 2003) which exceeded the technical resources available in the current study.

2. Methods

2.1. Subjects

Eighteen un-medicated subjects (all males) with AS frequenting the outpatient care of Vadaskert Child Psychiatric Hospital, Budapest and 14 control (CONT) subjects were recruited in a multicentre sleep study. Parents of the participating children and subjects above the age of 18 years signed the informed consent approved by the ethics committee of Semmelweis University, Budapest, Hungary. Principles of the Declaration of Helsinki were followed. Parents were interviewed extensively with respect to all behavioural and cognitive characteristics of their children. All subjects went though a comprehensive clinical assessment. The diagnosis of AS was based on ICD-10 criteria, and also confirmed by the Autism Diagnostic Observation Schedule (ADOS) criteria and performed by experienced clinicians from the Autism Foundation and Research Group, Budapest. All subjects with AS participated in regular meetings for special education purposes in the framework of the Vadaskert Child Psychiatric Hospital. No subject had a history of verbal language delay, any neurological, or co-morbid psychiatric disorder. No subject exhibited spike wave EEG activity. No subjects with reported sleep problems were enrolled in the study.

Subjects were matched in non-verbal IQ [mean Raven's Progressive Matrices row score CONT: 49.9 (SD = 6.5) vs. AS: 51 (SD = 8.8), $t = 0.34$, $P = 0.741$], gender and lateralization. There was a statisti-

cally non-significant difference between the mean age of the groups [mean age expressed in months, CONT: 177 (SD = 41), age range: 90–260 vs. AS: 158 (SD = 48), age range: 108–260; t = 1.67, P = 0.253].

The subjects (8 patients with AS) assessed in the sleep laboratory of the Institute of Behavioural Sciences, Semmelweis University were included only in the macrostructural sleep analyses, because the EEG references and sampling rate was slightly different between the two laboratories. This could possibly have affected spectral and coherence indices. The spectral and coherence analysis was based on a sample of 24 subjects (14 CONT and 10 AS) assessed in the sleep laboratory of the Vadaskert Child Psychiatric Hospital. The age [CONT: 177 (SD = 41) vs. AS: 150 (SD = 52); t = 1.41, P = 0.172] and IQ [CONT: 49.9 (SD = 6.5) vs. AS: 52.9 (SD = 5.4); t = 0.97, P = 0.340] matching between control and patient groups in this sub-sample was similar to that of the combined sample.

2.2. Measures

EEG, EOG, EMG and ECG were recorded on two consecutive nights. A 10 channel (F3, F4, C3, C4, P3, P4, T3, T4, O1, O2) EEG montage was used. Ag/AgCl electrodes were fixed with EC Grass electrode gel. In one of the laboratories (Semmelweis University) signals were collected, pre-filtered, amplified and digitized at a sampling rate of 249 Hz/channel by using the 30 channel Flat Style SLEEP La Mont Headbox with implemented second order filters at 0.5 Hz (high pass) and 70 Hz (low pass) as well as the HBX32-SLP 32 channel preamplifier (La Mont Medical Inc. USA). In the other sleep laboratory (Vadaskert Child Psychiatric Hospital) a physically linked mastoid reference was applied. By using a BQ 132S Aquisition Headbox (Micromed, Italy) for polysomnographic data recording EEG and polygraphic data was high-pass filtered at 0.33 Hz and low-pass filtered at 1500 Hz by a 40 dB/decade anti-aliasing hardware input filter. Data were collected with 12 bit resolution and with an analogue to digital conversion rate of 4096 Hz/channel (synchronous). A further 40 dB/decade anti-aliasing digital filter was applied by digital signal processing which low-pass filtered the data at 120 Hz. After this the digitized and filtered EEG was subsequently undersampled at 256 Hz and then subjected to spectral and coherence analyses.

PSG assessment was performed by the same specialists and by the use of standard procedures in both laboratories. The timing of lights off was determined by subjects' sleep–wake habit, and the awakenings were spontaneous.

The first night served as an adaptation period to the sleep laboratory conditions. The EEGs obtained during the second night EEG recording were visually scored by an experienced scorer (ASL), with an epoch length of 20 s according to standard criteria (Rechtschaffen and Kales, 1968). After visual artefact rejection, stages 2, 3 and 4 of NREM sleep were subjected to spectral and coherence analyses. The spectra and coherences were calculated by Welch's periodogram method using 4 s long non-overlapping epochs each linearly detrended. A 1024 point Hanning window was applied to minimize leakage. The calculations were done in the Python programming language (Python, 2009) using the SciPy and Matplotlib packages. The power spectrum density was computed by the following function call:

```
freq, spec = matplotlib.mlab.psd(

    signal, # input data vector
    NFFT = 1024, # 4 s epoch
    Fs = 256, # sampling frequency
    window = numpy.hanning(NFFT),
    detrend = matplotlib.mlab.detrend_linear,
    overlap = 0),
```

where freq contains the frequencies while spec the return values for the spectral density. The function for coherence (cohere) has the same arguments only with two input data vectors instead of one.

Absolute and relative power spectrum density (PSD) and coherence indices were computed for the delta (0.5–4 Hz), theta (4.25–7.75 Hz), alpha (8–10.75 Hz), sigma (11–15 Hz), beta (15.25–25 Hz), gamma 1 (25.25–35 Hz) and gamma 2 (35.25–45 Hz) frequency bands. The standard frequency bands were assigned in accordance with previous studies (e.g. Ferri et al., 2000).

Because there are only a low number of data points in most of these intervals (4 points/Hz) the average spectral density if calculated by simple summation is very sensitive to minuscule shifts in the band boundaries. In order to eliminate this discontinuous dependence, reduce the sensitivity of the average to the band limits and make the method robust, the averaging was performed by integrating numerically the linearly interpolated spectrum (and coherence) over the different regions. The used functions were:

```
spl = scipy.interpolate.splrep(freq, spec, k = 1)

average = scipy.interpolate.splint(f_low, f_high,
spl)/(f_high−f_low),
```

where f_low and f_high are the limits of the frequency region. The gained absolute and relative PSD data from the ten derivations were grouped into six regions along a sagital-Region (sRegion: frontal, centro-temporal, and posterior) and Hemisphere factor (left and right) and averaged over each region so as to reduce the number of statistical comparisons. Thus the regions were left frontal (F3), right frontal (F4), left centro-temporal (C3, T3), right centro-temporal (C4, T4), left posterior (P3, O1), and right posterior (P4, O2), respectively (Fig. 1).

In order to analyze intrahemispheric coherence we employed the same two factors (sRegion and hemisphere) averaging coherence data from all intrahemispheric electrode pairs related to a specific area. Thus the regions were left frontal (F3–C3, F3–T3, F3–P3, F3–O1), right frontal (F4–C4, F4–T4, F4–P4, F4–O2), left centro-temporal (F3–C3, C3–T3, C3–P3, C3–O1, F3–T3, T3–P3, T3–O1), right centro-temporal (F4–C4, C4–T4, C4–P4, C4–O2, F4–T4, T4–P4, T4–O2), left posterior (F3–P3, T3–P3, C3–P3, P3–O1, F3–O1, C3–O1, T3–O1), and right posterior (F4–P4, T4–P4, C4–P4, P4–O2, F4–O2, C4–O2, T4–O2), respectively. In the case of interhemispheric coherence we implicitly created only a sRegion factor averaging coherence data across all interhemispheric electrode pairs related to the specific sagital area. Consequently there was a frontal (F3–F4, F3–C4, F3–T4, F3–P4, F3–O2, F4–C3, F4–T3, F4–P3, F4–O1), a centro-temporal (F4–C3, C3–C4, C3–T4, C3–P4, C3–O2, F3–C4, C4–T3, C4–P3, C4–O1, F4–T3, C4–T3, T3–T4, T3–P4,T3–O2, F3–T4, C3–T4, T4–P3,T4–O1) and a posterior (F4–P3, C4–P3, T4–P3, P3–P4, P3–O2, F3–P4, C3–P4, T3–P4, P4–O1, F4–O1, C4–O1, T4–O1, P4–O1, O1–O2, F3–O2, C3–O2, T3–O2, P3–O2) sagital-Region (Fig. 1).

2.3. Statistical analyses

2.3.1. Group comparisons

Although the studied groups were comparable and there was only a slight and statistically non-significant difference in age, we nevertheless used age as a co-variate in all statistical analyses concerning quantitative EEG measures in order to minimize the bias caused by this confounding factor in the assessment of inter-group differences with respect to EEG power and coherence (see Supplementary data; S1).

Statistical analyses for spectral measures were applied in two consecutive steps. First, we employed multivariate analysis of covariance in order to analyze group differences in absolute and
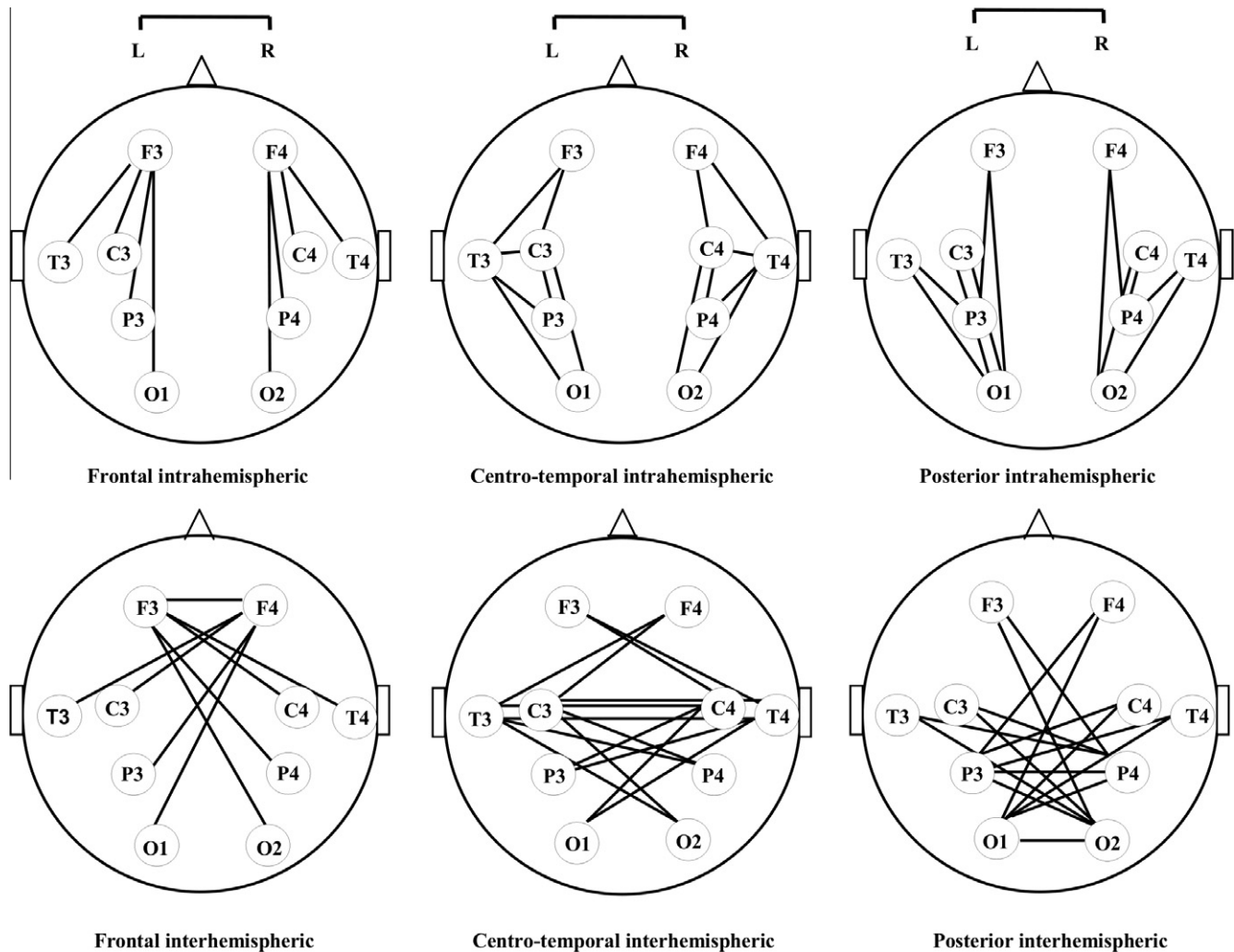
Fig. 1. Graphical representations of the regions created for coherence analyses. The upper panels represents regions created along the factors sagital-Region (frontal, centro-temporal, posterior) and Hemisphere (left, right) which were used for the statistical analysis of intrahemispheric coherence. The bottom panels represents regions created along the factor sagital-Region (frontal, centro-temporal, posterior) which were used for the statistical analysis of interhemispheric coherence. Regions are created by averaging coherence values among electrode pairs related to a certain region.

relative power spectrum density for the entire frequency range (absolute total power) and then for each frequency band separately. In these analyses we focused on the main effects of factor Group (between factor: Control and AS) and on interactions between factor Group, factor sagital-Region (sRegion: frontal, centro-temporal, and posterior) and factor Hemisphere (left and right) within factors (2 Groups × 3 sRegions × 2 Hemispheres). If significant ($P < 0.05$) interactions emerged we used post hoc Fisher Least Significance Difference (LSD) tests to explore whether the observed sRegion and/or Hemisphere factor dependent group differences were statistically significant ($P < 0.05$) or not.

The statistical analyses of coherence was also performed in several consecutive steps progressing from 'global' to 'local' effects with respect to both frequency and topography. In the first step focusing at the entire frequency range (0.5–45 Hz) we used a multivariate model including the between factor Group and two within factors: sRegion (frontal, centro-temporal, posterior) and Type of coherence (inter- or intrahemispheric). In the next step still focusing upon the entire frequency range we analyzed group differences in intrahemispheric coherence including in the multivariate model the between factor Group and the within factors sRegion and Hemisphere (left and right).

In a subsequent exploratory analysis we assessed group differences of inter- and intrahemispheric coherence measures for each

frequency band separately. Here we looked at the above mentioned interactions (interhemispheric coherence: Group × sRegion; intrahemispheric coherence: Group × sRegion × Hemisphere). If significant interactions emerged we performed post hoc Fisher LSD tests to analyze the group differences in more detail.

In a final step we aimed to identify the specific subregion (electrode pair) contributing to a specific regional group difference. This was purposeful, because the regions employed in the multivariate models consisted of averaged values of coherence indices belonging to a higher number of electrode pairs. Thus we aimed to delimit the cortical subregion showing to be mostly different in between the groups. For this purpose we applied univariate analysis of covariance. In order to avoid the increased risk of type I error due to multiple comparisons we resorted to Bonferroni-type corrections. That is we set the α for the entire set n comparisons (number of electrode pairs included in the analyzed region × 7 frequency bands) (by taking the alpha value for each comparisons) equal to $0.05/n$.

It is important to mention that the average coherence values across all electrode pairs within a region are biased toward the closest electrode pairs within the same region because of volume conduction. This, however, should not lead to any change in the significance of the group differences.

Statistical analyses were performed using STATISTICA 7. (StatSoft Inc. USA) and SPSS 15.0.1 for Windows (SPSS, Inc. USA).

3. Results

3.1. Sleep macrostructure

The AS group spent significantly more time in bed, had a longer sleep onset latency, a somewhat lower sleep efficiency and longer wake after sleep onset. Differences in SWS between the AS and controls were not statistically significant (Table 1). These differences between AS and controls were not statistically significant in the data set used for the qEEG analyses, although the numerical differences were in the same direction.

3.2. Absolute power spectrum density

Analyses of the absolute total PSD revealed neither a main effect for the factor Group nor any interaction. Analyses of PSD per frequency band revealed a significant overall decrease in alpha $[F(1,21) = 5.232, P = 0.033]$, sigma $[F(1,21) = 4.725, P = 0.041]$, beta $[F(1,21) = 4.497, P = 0.046]$, gamma 1 $[F(1,21) = 8.078, P = 0.01]$, and gamma 2 $[F(1,21) = 10.772, P = 0.004]$ in the AS group compared to controls (Fig. 2). We observed a considerable overall increase in delta power in AS $[F(1,22) = 5.634, P = 0.027]$, which after controlling for age was no longer significant $[F(2,42) = 3.632, P = 0.07]$.

3.3. Relative power spectrum density

As shown in Fig. 3 relative delta PSD exhibited a significant main effect for the factor Group $[F(1,21) = 12.067, P = 0.002]$ for delta, pointing to an overall increase of the relative spectral power in AS group compared to the Controls. Furthermore, a significant interaction between the factors Group and sRegion in the sigma $[F(2,42) = 4.875, P = 0.012]$ and beta $[F(2,42) = 5.252, P = 0.011]$ frequency bands emerged. Post hoc analysis revealed a significant decrease of relative sigma PSD over the frontal $(P = 0.02)$, and of relative beta PSD over the centro-temporal $(P = 0.025)$ areas. Please note that in all of these analyses age was used as a co-variate.

3.4. Coherence

3.4.1. Entire frequency band

In the first step, analyzing group differences in coherence with respect to the entire frequency range we found a significant Group × sRegion × Type of coherence interaction $[F(2,42) = 3.315,$

$P = 0.046]$. Post hoc analysis revealed significantly lower values of intrahemispheric coherence over the frontal region $(P = 0.032)$ in the AS group compared to Controls, while interhemispheric coherence was not significantly different between the groups (Fig. 4).

In the second step, analyzing group differences in intrahemispheric coherence over the entire frequency range, we found a significant interaction between the factors Group and sRegion $[F(2,42) = 3.896, P = 0.028]$ and the factors Group and Hemisphere $[F(1,21) = 5.667, P = 0.027]$. As shown in Fig. 5, Fisher LSD Post hoc analyses revealed significantly lower values of intrahemispheric coherence in AS compared to the Controls over the frontal $(P = 0.015)$ region and the right hemisphere $(P = 0.033)$.

3.4.2. Individual frequency bands

Based on above presented significant group differences involving only the intrahemispheric coherence, we next analyzed group differences and interactions solely for this type of coherence measure, addressing each frequency band separately for exploratory purposes (Table 2). We found recurrent significant interactions between the factors Group and sRegion in each frequency range: delta $[F(2,42) = 3.644, P = 0.035]$, theta $[F(2,42) = 3.786, P = 0.031]$, alpha $[F(2,42) = 3.625, P = 0.035]$, sigma $[F(2,42) = 4.181; P = 0.022]$, beta $[F(2,42) = 3.466, P = 0.040]$, gamma 1 $[F(1,21) = 3.348, P = 0.045]$, and gamma 2 $[F(2,42) = 3.358, P = 0.044]$. We also observed significant interactions between the factors Group and Hemisphere in the delta $[F(1,21) = 9.949, P = 0.005]$, theta $[F(1,21) = 4.567, P = 0.045]$, sigma $[F(1,21) = 5.505, P = 0.029]$, gamma 1 $[F(1,21) = 4.584, P = 0.044]$, and gamma 2 $[F(1,21) = 5.641, P = 0.027]$ frequency bands.

Post hoc analysis revealed significantly lower intrahemispheric coherence values in AS compared to the Controls over the frontal region in delta $(P = 0.006)$, theta $(P = 0.018)$, alpha $(P = 0.012)$, sigma $(P = 0.016)$ and beta $(P = 0.048)$, as well over the right hemisphere in delta $(P = 0.019)$ and sigma $(P = 0.016)$ frequency bands (Table 2).

3.5. Univariate analysis of coherence

Using univariate analysis of covariance we computed group differences along the electrode pairs belonging to the affected regions as revealed by the multivariate analysis of covariance. Because all significant differences along the factor sRegion emerged exclusively over the frontal region we included all intrahemispheric electrode pairs related to this region (F3–C3, F3–T3, F3–P3, F3–O1, F4–C4, F4–T4, F4–P4, F4–O2) in the analysis. We found significantly lower $(P < 0.002)$ coherence values in the left (F3–C3) and right (F4–C4) fronto-central areas with respect to the entire frequency band (0.5–45 Hz). Subsequently we also analyzed group differences along each frequency band. After we applied Bonferroni correction for the 56 comparisons (8 channels × 7 frequency bands) we found significantly decreased intrahemispheric coherence values over the F4–C4 area in delta $(P = 0.004)$, theta $(P = 0.017)$, and sigma $(P = 0.001)$ as well as in the F3–C3 region in alpha $(P = 0.049)$ and sigma $(P = 0.030)$ frequency bands (Table 3).

4. Discussion

This is a first study in which whole night NREM sleep dependent EEG spectra and its topography as well as phase coherence in children and adolescents with AS is compared with age and IQ matched controls. Marked changes in both absolute and relative power density values as well as changes in intrahemispheric coherence were observed in AS. In the following we discuss our results in the light of the available data in ASD. Because AS represents

Table 1
Polysomnographic data of controls and Asperger subjects.

	Control (N = 14)		Asperger (N = 18)		t-test
	Mean	SD	Mean	SD	P values
TIB (min)	519.7	78.6	572.9	58.4	0.036*
SPT (min)	493.6	74.4	507.9	60.3	ns
SE (%)	95.1	3.7	88.8	7.1	0.003*
SOL (min)	11.7	8.4	33.4	24.9	0.002*
WASO (min)	16.1	14.5	31.6	23.1	0.025*
S1 (min)	21.1	8.8	22.9	11.5	ns
S1 (%)	4.4	1.9	4.4	2.1	ns
S2 (min)	264.1	38.4	262.5	37.5	ns
S2 (%)	53.6	3.6	51.8	5.6	ns
SWS (min)	83.3	21.4	99.4	27.7	0.073
SWS (%)	16.8	3.4	19.7	5.9	0.085
REM (min)	124.9	27.5	122.9	29.3	ns
REM (%)	25.2	3.5	24.1	3.9	ns
REM latency (min)	105.9	50.1	89.9	34.9	ns

Mean values and standard deviations (SD) are presented with P values indicating the 2 tailed significance level of group differences. TIB = time in bed; SPT = sleep period time; SE = sleep efficiency; SOL = sleep onset latency; WASO = waking after sleep onset; S1 and S2 = NREM sleep stages 1 and 2; SWS = slow-wave sleep; REM = rapid eye movement sleep.
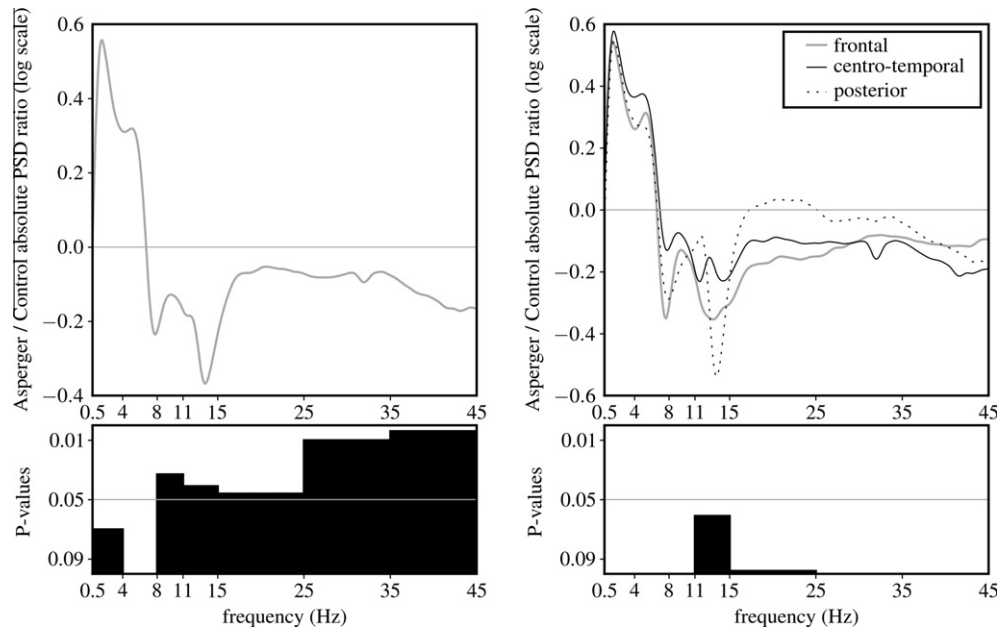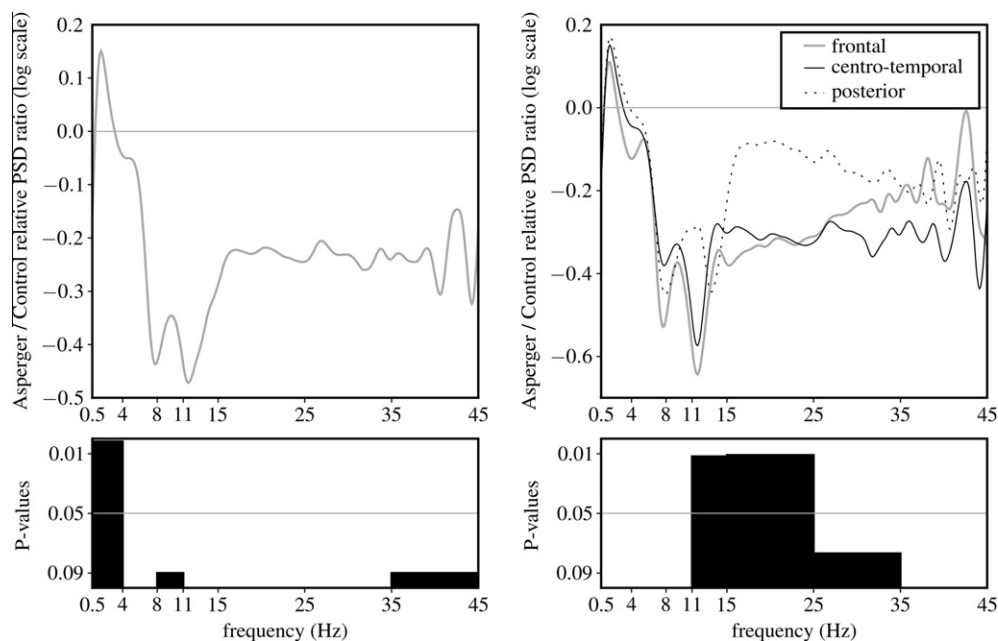
Fig. 2. EEG absolute power spectral density in Asperger, expressed relative to Controls across each frequency band. The upper plots represent the ratio between the power spectral densities for the two groups calculated using the geometric averages over all subjects in the respective groups. The horizontal reference line at 0 reflects mean absolute spectral power density values for the Control group. Smoothing is applied with a 20 point Hanning window. Plots in the bottom panels reflect the levels of significance (P values) with respect to Group main effects (averaging over all channels) (left figure) and Group vs. sagital-Region (interactions averaging over each main sagital-Region: frontal, centro-temporal, posterior) (right figure).
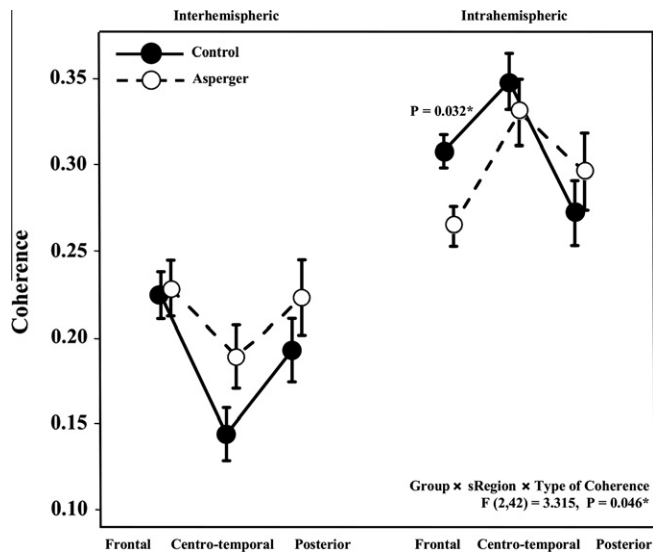
only one segment of the autistic spectrum, our inferences and interpretations based on studies in which different or uncontrolled ASD subtypes were studied, need to be cautious.

Our observations of increased sleep onset latency, waking after sleep onset and decreased sleep efficiency in subjects with AS are in accordance with previous reports of sleep problems in children and adolescents with ASD (Lázár and Bódizs, 2008). Our sleep effi-

ciency score in AS (88.8%) is similar to the value of 88.2% which was reported in younger children with ASD who were good sleeper (Malow et al., 2006) or without a reported altered sleep pattern, 89% (Miano et al., 2007), and is slightly higher than in children with AS in a similar age range, 86% (Bruni et al., 2007). The magnitude of the observed differences in wake after sleep onset and sleep efficiency are also relatively minor when compared to for

Fig. 3. EEG relative power spectral density in Asperger, expressed relative to Controls across each frequency band. The upper plots represent the ratio between the relative power spectral densities for the two groups calculated using the geometric averages over all subjects in the respective groups. The horizontal reference line at 0 reflects mean relative spectral power density values for the Control group. Smoothing is applied with a twenty point Hanning window. Plots in the bottom panels reflect the levels of significance (P values) with respect to Group main effects (averaging over all channels) (left figure) and Group vs. sagital-Region (interactions averaging over each main sagital-Region: frontal, centro-temporal, posterior) (right figure).

Fig. 4. Group differences in inter- and intrahemispheric coherence. Interaction between factors Group, sagital-Region (sRegion) (frontal, centro-temporal, posterior) and Type of coherence (inter- vs. intrahemispheric) in the entire analyzed frequency range (0.5–45 Hz). Least squares means are presented. Vertical bars denote standard errors; Exposed *P* values above figure reflect significance level of group differences according to Fisher LSD post hoc analysis.

ing disorders or periodic limb movements exist between the groups and that these differences contribute to differences in sleep structure. The AS group presented with significantly higher anxiety scores on the Child Behaviour Checklist (CBCL). Anxiety may also have contributed to the reduction in sleep efficiency in this clinical group. Although it is unlikely, it cannot be ruled out that this may have impacted the spectral data as well.

The differences in PSG measures such as sleep efficiency are very unlikely to have directly affected the results of the power spectral and coherence analyses because these analyses were based on stage 2, 3 and 4 NREM sleep.

Spectral analysis revealed a region independent overall increase of the relative delta activity in AS compared to controls coupled with a regional decrease of the relative frontal sigma, and centro-temporal beta, respectively. In addition we observed a significant region independent overall decrease of the absolute spectral density across a large frequency range (8–45 Hz). These differences cannot be attributed to the non-significant differences in age between the groups because we used age as a co-variate in all analyses. The interpretation of the spectral results is fairly difficult because of the paucity of quantitative sleep EEG studies in ASD or related child neuropsychiatric disorders. Previous PSG studies reported decreased slow-wave sleep (Limoges et al., 2005) as well as a non-significant reduction of delta activity in young adults with AS (Tani et al., 2004). However, these studies were carried out in older subjects compared to our groups, and this might account for the distinct slow wave activity (SWA) profile reported here. This is reasonable considering that AS is a neurodevelopmental condition showing a different pattern of brain maturation during development (see a review in Frith, 2003). Another recent PSG study investigating children within an age range similar to our participants reported an increase in sleepiness, and in the percentage of synchronized A1 phase of CAP in children with AS compared to age matched controls (Bruni et al., 2007). This observation may be in accordance with our results because sleepiness and synchronized A1 phase of CAP have both been related to EEG activity characterised by a spectral peak in the low frequency range, prevailing over the frontal region (Cajochen et al., 1999; Ferri et al., 2005).

In normal developing children and adolescents, delta and theta activity were shown to correlate inversely with brain maturation consistent with a gradual decrease of synaptic density presumably
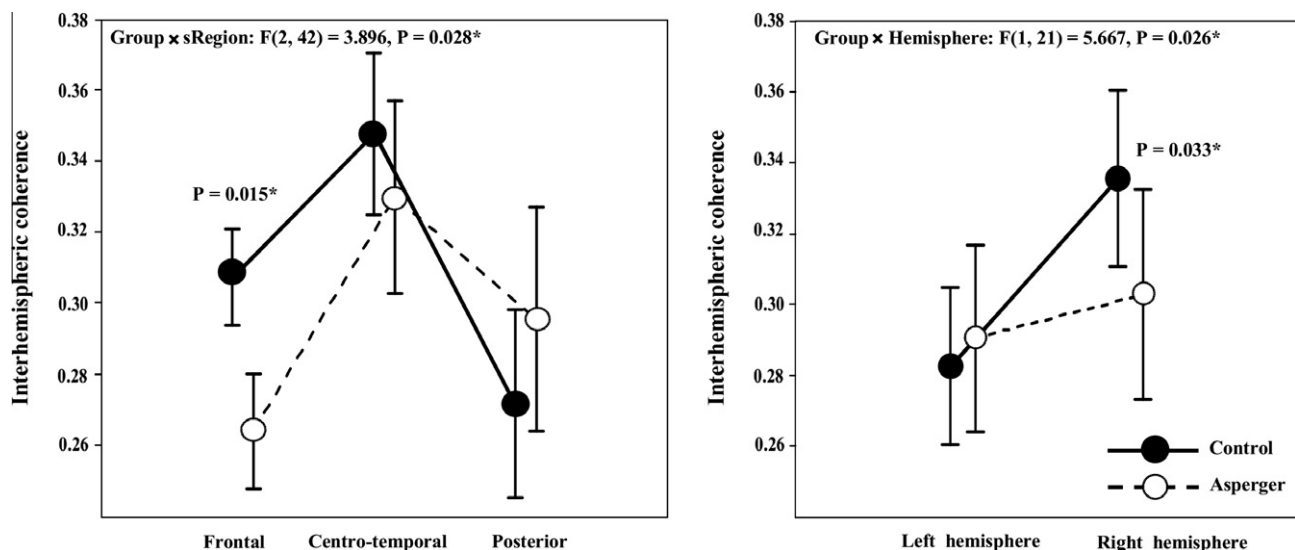
example age-related changes in sleep. The relatively minor differences between AS and controls with respect to PSG measures is also reflected in the loss of statistical significance when the analyses of these data was restricted to the subgroup in which the qEEG analyses was performed. The fact that the significance of group differences did not persist when the analyses restricted to this subgroup should not be interpreted as implying that this subgroup was not representative. In fact, a direct comparison of the two autistic groups studied in the two laboratories showed no significant differences in any of the sleep macrostructure measures. The subjects were not reported to have sleep problems, but in neither the controls nor the AS did we measure leg movements and breathing patterns in order to increase compliance. Thus we cannot rule out the possibility that differences in sleep related breath-

Fig. 5. Group differences in intrahemispheric coherence. Least squares means of intrahemispheric coherence values for the entire frequency range and for each frequency band in both groups. Interaction between factor Group, factor sagital-Region (frontal, centro-temporal, posterior) and factor Hemisphere (inter- vs. intrahemsipheric) in the entire analyzed frequency range (0.5–45 Hz). Vertical bars indicate standard errors; *P* values reflect the significance level of group differences according to Fisher LSD post hoc analysis.

Table 2
Coherence data.

	Group	Intrahemispheric coherence					Interhemispheric coherence		
		Factor sRegion			Factor hemisphere		Factor sRegion		
		Front	Cent-temp	Post	Left hem	Right hem	Front	Cent-temp	Post
All freq.	CONT	**0.31 (0.06)**	0.35 (0.07)	0.28 (0.07)	0.29 (0.06)	**0.34 (0.07)**	0.23 (0.05)	0.15 (0.05)	0.20 (0.06)
	AS	**0.25 (0.04)**	0.32 (0.08)	0.29 (0.08)	0.28 (0.07)	**0.29 (0.06)**	0.22 (0.05)	0.18 (0.08)	0.21 (0.1)
Delta	CONT	**0.37 (0.06)**	0.41 (0.08)	0.31 (0.08)	0.34 (0.07)	**0.39 (0.07)**	0.32 (0.06)	0.23 (0.06)	0.29 (0.07)
	AS	**0.30 (0.06)**	0.38 (0.08)	0.32 (0.09)	0.33 (0.06)	**0.34 (0.06)**	0.31(0.07)	0.27 (0.09)	0.30 (0.11)
Theta	CONT	**0.36 (0.04)**	0.39 (0.06)	0.28 (0.05)	0.32 (0.05)	0.37 (0.05)	0.30 (0.05)	0.18 (0.04)	0.23 (0.04)
	AS	**0.30 (0.05)**	0.36 (0.06)	0.30 (0.08)	0.31 (0.04)	0.33 (0.06)	0.29 (0.06)	0.22 (0.07)	0.24 (0.09)
Alpha	CONT	**0.33 (0.05)**	0.37 (0.06)	0.26 (0.06)	0.29 (0.05)	0.34 (0.05)	0.27 (0.07)	0.16 (0.06)	0.20 (0.05)
	AS	**0.27 (0.05)**	0.34 (0.07)	0.28 (0.08)	0.29 (0.06)	0.31 (0.05)	0.26 (0.07)	0.19 (0.09)	0.20 (0.11)
Sigma	CONT	**0.37 (0.05)**	0.39 (0.07)	0.34 (0.06)	0.33 (0.06)	**0.40 (0.05)**	0.23 (0.06)	0.16 (0.05)	0.24 (0.06)
	AS	**0.31 (0.04)**	0.35 (0.07)	0.35 (0.07)	0.33 (0.06)	**0.34 (0.05)**	0.25 (0.06)	0.20 (0.08)	0.24 (0.10)
Beta	CONT	**0.26 (0.07)**	0.31 (0.07)	0.24 (0.07)	0.25 (0.06)	0.29 (0.07)	0.16 (0.08)	0.10 (0.07)	0.14 (0.06)
	AS	**0.21 (0.04)**	0.28 (0.08)	0.26 (0.09)	0.24 (0.06)	0.26 (0.06)	0.16 (0.06)	0.13 (0.08)	0.16 (0.11)
Gamma 1	CONT	0.25 (0.06)	0.30 (0.08)	0.25 (0.09)	0.24 (0.07)	0.29 (0.08)	0.16 (0.06)	0.10 (0.06)	0.15 (0.07)
	AS	0.20 (0.03)	0.27 (0.08)	0.25 (0.09)	0.23 (0.06)	0.25 (0.07)	0.14 (0.05)	0.12 (0.08)	0.16 (0.11)
Gamma 2	CONT	0.27 (0.08)	0.31 (0.10)	0.26 (0.11)	0.26 (0.09)	0.30 (0.10)	0.17 (0.09)	0.12 (0.10)	0.18 (0.11)
	AS	0.20 (0.04)	0.26 (0.08)	0.25 (0.09)	0.23 (0.06)	0.24 (0.08)	0.13 (0.04)	0.12 (0.07)	0.16 (0.10)

Mean coherence values for the created regions along the factors sagital-Region (sRegion) and Hemisphere for the Control (CONT, $n = 14$) and Asperger (AS, $n = 10$) groups (SD in brackets). Bolded numbers reflect mean coherence values that were significantly different between groups according to Fisher LSD Post hoc analysis. Post hoc analyses were performed only if significant interactions were observed. Front = frontal; cent-temp = centro-temporal; post = posterior; left hem = left hemisphere; right hem = right hemisphere; All freq. = 0.5–45 Hz.

caused by an age-programmed synaptic pruning that decreases waking brain metabolic rate (Campbell and Feinberg, 2009). The decline of delta and theta activity in NREM sleep emerges most abruptly in adolescence due to an escalated brain maturation indexed by synaptic pruning (Campbell et al., 2007) and begins later in boys than in girls (Campbell et al., 2005) suggesting a delayed maturation of the male brain. According to neurobiological and neuropsychological assessments children with ASD may be characterised by delayed brain maturation due to a possible pruning disorder leading to an increased synaptic density and disconnectivity (Frith, 2003) and thereby increased delta activity. Although this interpretation is attractive it is not supported by the fact that the intelligence measures were fairly similar in the two groups.

An alternative interpretation of the observed increase in delta activity relates to association between changes in delta activity and sleep loss. The increased relative delta as well as the decreased relative sigma activity in the patient group is reminiscent of the effects of sleep deprivation on the EEG and may suggest an elevated sleep propensity in AS (Dijk et al., 1993; Jenni et al., 2005). The time course of sigma activity and spindle density across subsequent cycles goes in an opposite direction from that of SWA (Ferri et al., 2000). It is important to mention that since we have not found a difference in the total power the significant increase in the relative delta in AS may be directly related to the significant decrease in the absolute high frequency activity (8–45 Hz).

Table 3
Frontal intrahemispheric coherence.

		All freq.	Delta	Theta	Alpha	Sigma	Beta	Gamma
	Group							
F3–T3	CONT	0.38 (0.09)	0.42 (0.1)	0.38 (0.1)	0.38 (0.1)	0.36 (0.12)	0.35 (0.12)	0.41(0.09)
	AS	0.36 (0.13)	0.38 (0.19)	0.37 (0.16)	0.36 (0.16)	0.35 (0.15)	0.32 (0.12)	0.39 (0.11)
F3–C3	CONT	**0.55 (0.07)**	0.65 (0.09)	0.65 (0.07)	**0.62 (0.08)**	**0.64 (0.06)**	0.48 (0.1)	0.39 (0.1)
	ASP	**0.43 (0.08)**	0.53 (0.11)	0.53 (0.08)	**0.49 (0.08)**	**0.52 (0.07)**	0.36 (0.09)	0.29 (0.09)
F3–P3	CONT	0.19 (0.05)	0.27 (0.09)	0.26 (0.06)	0.19 (0.05)	0.26 (0.05)	0.11 (0.06)	0.12 (0.08)
	AS	0.15 (0.04)	0.21 (0.07)	0.2 (0.06)	0.15 (0.07)	0.23 (0.07)	0.08 (0.04)	0.08 (0.04)
F3–O1	CONT	0.04 (0.03)	0.05 (0.04)	0.03 (0.02)	0.02 (0.02)	0.07 (0.04)	0.02 (0.02)	0.06 (0.07)
	AS	0.04 (0.02)	0.04 (0.03)	0.03 (0.02)	0.02 (0.02)	0.08 (0.05)	0.02 (0.02)	0.04 (0.03)
F4–T4	CONT	0.40 (0.09)	0.5 (0.1)	0.45 (0.1)	0.44 (0.09)	0.43 (0.09)	0.34 (0.12)	0.33 (0.12)
	AS	0.32 (0.11)	0.4 (0.15)	0.39 (0.15)	0.37 (0.14)	0.35 (0.15)	0.27 (0.09)	0.25 (0.06)
F4–C4	CONT	**0.65 (0.08)**	**0.71 (0.07)**	**0.72 (0.07)**	0.7 (0.09)	**0.72 (0.06)**	0.59 (0.11)	0.56 (0.11)
	AS	**0.51 (0.06)**	**0.55 (0.06)**	**0.59 (0.07)**	0.57 (0.07)	**0.58 (0.06)**	0.46 (0.09)	0.41 (0.08)
F4–P4	CONT	0.25 (0.08)	0.33 (0.1)	0.32 (0.07)	0.25 (0.08)	0.34 (0.08)	0.16 (0.1)	0.18 (0.11)
	AS	0.19 (0.06)	0.25 (0.06)	0.26 (0.07)	0.21 (0.08)	0.28 (0.06)	0.12 (0.06)	0.12 (0.07)
F4–O2	CONT	0.05 (0.03)	0.06 (0.04)	0.04 (0.02)	0.02 (0.02)	0.1 (0.04)	0.02 (0.03)	0.06 (0.08)
	AS	0.04 (0.03)	0.04 (0.03)	0.04 (0.04)	0.03 (0.03)	0.09 (0.05)	0.03 (0.04)	0.04 (0.05)

Mean intrahemispheric coherence values belonging to each electrode pair in the frontal region for the Control (CONT, $n = 14$) and Asperger (AS, $n = 10$) groups (SD in brackets). Bolded numbers reflect mean coherence values where significant group differences emerged after Bonferroni correction. All freq. = 0.5–45 Hz; Gamma (mean values of Gamma 1 and Gamma 2) = 25–45 Hz.

It is also important to mention that the sigma activity has been related to spindle activity during NREM sleep reported to be decreased in AS (Godbout et al., 2000; Limoges et al., 2005). Sleep spindles reflect thalamo-cortical resonance (Steriade, 2006) a system possibly affected in AS (Tsatsanis et al., 2003; Hardan et al., 2006; Limoges et al., 2005). The frontal decrease of the relative sigma activity may be related to a frontal region specific deficit in the thalamo-cortical resonance. Furthermore, the overall decrease of the absolute alpha, beta and gamma EEG power and the centro-temporal relative beta power in the AS group is intriguing, but the interpretation is not straightforward. The most significant reduction emerged in the gamma frequency bands. Short-range gamma synchronization has been proposed to underlie perceptual binding (Singer, 2002), long range coupling of cortical areas has been proposed to subserve the integration of cognitive processes (Miltner et al., 1999). Gamma rhythms are part of background neural activity related to a variety of non-conscious, cortical processes during wakefulness and are also present during sleep and anaesthesia (Steriade et al., 1996). Spontaneous gamma oscillations have been explained by cortical and thalamo-cortical resonant synaptic interactions (Llinás and Ribary, 1993). Although there are a large number of studies related to the significance of waking gamma activity in neuropsychiatric disorders (Herrmann and Demiralp, 2005) there is a paucity of data on gamma activity during sleep. However, we assume that the significant decrease in activity of the high frequency EEG bands may reflect another aspect of the altered cortico-cortical and thalamo-cortical resonance hypothesized in ASD (Tsatsanis et al., 2003; Hardan et al., 2006; Limoges et al., 2005).

The most robust result we observed was the significant intra-hemispheric coherence decrease across a large range of frequencies in the experimental group compared to the control one emerging over the frontal region, and over the right hemisphere. The reduction of spectral power in AS, which was observed over a broad frequency range, but not in the delta and theta band, may have contributed to the reduced intrahemispheric coherence in the higher frequency bands (alpha to gamma 2) due to volume conduction (Nunez et al., 1997). However, this would not be expected to affect decreased coherence in the delta and theta frequency bands.

Our data of reduced intrahemispheric coherence is in accordance with a recent study of the daytime resting EEG during eyes closed study which reported a significant dysfunctional integration of frontal and posterior brain regions in children with autistic spectrum disorder along with a pattern of neural underconnectivity (Coben et al., 2008). However, in contrast to this study we only found significant difference in intrahemispheric coherence measures and not in interhemispheric measures. This could be due to the different neurophysiological mechanisms engaged by the sleeping brain as compared to wakefulness and also to the clinical subgroup of ASD envisaged in the study. In accordance with Coben et al. (2008), we also found a greater number of significant differences in the coherence vs. power domains. This may suggests that neural organization and connectivity as reflected in changes in coherence may be a primary dysfunction of the autistic brain (Coben et al., 2008). The robust intrahemispheric coherence decrease in the bilateral fronto-central areas reflecting a fronto-cortical underconnectivity points to this brain region as an area which is most affected in children with AS. Functional brain imaging has provided evidence that activation in the bilateral dorsolateral prefrontal cortex is associated with several executive functions (Elliott, 2003). This may be related to the currently reported reduced coherence over these areas possibly reflecting neurobiological alterations underpinning executive dysfunctions described in AS (Hill and Bird, 2006). The reported reduced coherence may also be in accordance with recent fMRI data revealing decreased fronto-posterior functional connectivity during tasks assessing executive functions (Koshino et al., 2008; Just et al., 2007), social cognition (Kana et al., 2008) visuo-motor performance (Villalobos et al., 2005) and also during restful wakefulness (Cherkassky et al., 2006) in subject with ASD. Furthermore, this brain area is also involved in the mirror neuron system proven to be affected in autistic children (Hadjikhani et al., 2006; Oberman et al., 2005). Our data of abnormal intrahemispheric vs. normal inter-hemispheric coherence may also be in accordance with a brain volumetric study in children with HFA reporting an increase of exclusively of the outer radiate white matter volume composed of intrahemispheric cortico-cortical connections with a frontal predominance (Herbert et al., 2004). The authors suggested an ongoing postnatal process involving white matter in autism that primarily affects intrahemispheric and cortico-cortical connections (Herbert et al., 2004). It is important to note, that the relevance of the above quoted research data for the present study is conceivable only in the broader concept of ASD since these studies employed mostly heterogenic subtypes of autistic conditions.

The marked right hemisphere reduction of intrahemispheric coherence reveals that the detected brain neural underconnectivity is considerably lateralized. This may be an AS specific sleep EEG marker in accordance with reports pointing to a possible right hemisphere disorder in this clinical category (Ellis and Gunter, 1999) due to a dysfunction of white matter affecting primarily the right hemisphere functioning (Gunter et al., 2002).

Some limitations of the study should be considered. Our study may be considered preliminary because of its sample size, which, even though it is larger than the sample size of many other studies in this research area, is still not very large. It is possible that with a bigger sample size more significant differences in spectral and coherence activity would have emerged (see Supplementary Data; S2). Furthermore, the age range of the sample is fairly broad and even though we statistically controlled for the effect of age upon the dependent variables, it may be argued that such a control is insufficient. This is because the brain development follows a nonlinear trend with aging and also because AS exhibits an altered brain developmental pattern compared to typically developing subjects (see Supplementary Data; S1). Our cross sectional study certainly cannot reveal the entire picture but may provide a useful starting point for future sleep studies in larger, more homogenous groups.

In conclusion, our sleep EEG findings indicate an altered brain connectivity pattern involving primarily the connection between the frontal region with other posterior cortical areas in children and adolescents with AS. This interpretation of these sleep EEG findings is in accordance with the underconnectivity hypothesis of autistic spectrum disorders (Just et al., 2004) affecting primarily the long-distance fronto-cortical connections (Courchesne and Pierce, 2005; Just et al., 2004).

However, this is the first study to provide evidence in this regard on the basis of an exhaustive linear quantitative analysis of whole night NREM sleep dependent oscillatory activity involving a large range of frequencies in children and adolescent with AS.

It would be of interest to study the sleep EEG in more populations and subtypes to assess whether these findings are either AS specific or rather related to the broader autistic phenotype.

5. Disclosure statement

This is not an industry supported study. The authors have indicated no financial conflicts of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2010.03.054.

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