ORIGINAL ARTICLE

Nonlinear analysis of the sleep EEG in children with pervasive developmental disorder

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Abstract

OBJECTIVES: Autism is a severe neurodevelopmental disorder with a high rate of epilepsy and subclinical epileptiform activity. High physical connectivity on a microcolumnar level leading to epileptiform activity and low functional informational connectivity are assumed in autism. The aim of this study was to investigate nonlinear EEG brain dynamics in terms of synchronization in a group of children with autism spectrum disorders compared to a control group. We expected a lower degree of synchronization in autistic subjects.

METHODS: The autistic group consisted of 27 patients with autism spectrum disorders diagnosed according to ICD-10. The mean age of the sample was 7.1 (SD 3.6) years, 14 of them were mentally retarded. Normal EEG was found in 9 patients, epileptiform EEG in 18 autistic patients. Four patients had a history of epileptic seizures, fully compensated in long term. The control group consisted of 20 children (mean age of 8.4, SD 2.3 years) with normal intelligence, without an epileptic history, investigated within the frame of the research program for cochlear implantation. They had normal neurological examination and suffered from perceptive deafness. Normal EEG was found in 17 of the control subjects, epileptiform EEG was in 3 control subjects. We analyzed night sleep EEG recordings from 10 channels (F3, F4, F7, F8, C3, C4, T3, T4, P3 and P4) with the inclusion of sleep stages NREM 2, 3 and 4 in the subsequent analyses. Coarse-grained entropy information rates between neighbouring electrodes were computed, expressing the synchronization between 11 selected electrode couples.

RESULTS: Synchronization was significantly lower in the autistic group in all three examined NREM stages even when age and intelligence were taken into account as covariates.

CONCLUSIONS: The results of the study confirmed the validity of the underconnectivity model in autism.

Abbreviations:

ANCOVA – Analysis of covariance
ASD – Autism spectrum disorders
CARS – Childhood Autism Rating Scale
CEI – Coarse-grained Entropy Information
CER – Coarse-grained Entropy Rate
CNS – Central nervous system
DSM-IV – Diagnostic and statistical manual of mental disorders (4^{th} ed.)
EEG – Electroencephalogram
ESES – Electrical status epilepticus character during slow-wave sleep
ICD-10 – International Statistical Classification of Diseases and Related Health Problems (10 th Revision)
MCIR – Mutual coarse-grained information rate
MEG – Magnetoencephalography
MESAN – Motol EEG System Analyses
MRI – Magnetic resonance imaging
fMRI – Functional magnetic resonance imaging
NREM – Non-rapid eye movement sleep
SD – Standard Deviation

INTRODUCTION

Childhood autism and other autism spectrum disorders (ASD) are currently conceived to be neurodevelopmental disorders and are defined by behavioural criteria in ICD-10 and DSM-IV. Delayed and deviant development in social and communication skills, restricted interests and stereotypical behaviour are the core symptoms, varying in their severity. About 75% of individuals with autism are mentally retarded (Saddock & Saddock, 1999). Despite considerable research efforts, no specific biological markers are yet known and the diagnosis of autism still risk being made late (Oslejskova *et al*. 2007). High rates of epilepsy (summarized median rate 16.7%) (Volkmar, 1998) and epileptiform EEG abnormalities (32–45%) (Cohen & Volkmar, 1997) in autism have been extensively reported. Some studies (Kawasaki *et al*. 1997; Hashimoto *et al*. 2001) found the epileptiform discharges predominantly in the frontal areas. A recent magnetoencephalographic study showed common specific abnormalities predominantly distributed in the perisylvian areas (Muñoz-Yunta *et al*. 2007). Epileptiform abnormalities in autism are probably not associated with the severity of autistic symptomatology (Hrdlicka *et al*. 2002), whereas autistic children with a history of epileptic seizures can exhibit more severe isolated symptoms, namely abnormal imitation and visual response (Kulisek *et al*. 2003).

Rubenstein and Merzenich (2003) developed a model of imbalance of the excitation/inhibition ratio in key neural systems resulting in epileptiform activity, which is supported by neuropathological findings of abnormal synaptic and microcolumnar structure (Casanova *et al*. 2002). In this sense, several authors have pointed out a local physical hyperconnectivity, linked with a high rate of epileptiform activity, and informational/functional underconnectivity in patients with ASD (Belmonte *et al*. 2004, Just *et al*. 2004, Courchesne & Pierce 2005). Current neurophysiological conceptions of autism content disrupted inter-regional cortical interactions. Lewis and Elman (2008) linked the development of aberrant connectivity patterns in autism spectrum disorders to the deviant brain growth trajectory in a dynamic neuronal network model study. Altered connectivity especially within the frontal areas and also in the fusiform face area, were documented by several studies involving different methods (e.g. fMRI, MEG, EEG). In a recent fMRI study of visual coding in autism, Koshino *et al*. (2008) revealed functional underconnectivity, specifically within frontal areas in the autism group but no underconnectivity among posterior cortical regions.

The binding process of synchronized and distributed activity is necessary for the mechanism of consciousness and seems to be altered in several psychiatric disorders, e.g. schizophrenia and dissociative processes (Bob, 2007). Informational processing is conditioned by high frequency gamma oscillations. Their production appears to be excessive in autism (Orekhova *et al*. 2007) while binding at high frequencies seems to be compromised, specifically in the left hemisphere (Wilson *et al*. 2006). Murias *et al*. (2007) found significant abnormalities in functional connectivity using EEG coherence in resting conditions in adults with ASD.

Dynamic connectivity within and between neuronal networks has been intensively studied (e.g. Brekspear, 2002; Brekspear & Terry, 2002; Stam *et al*. 2003; Volgushev *et al*. 2006). In Friston's integrative model (Friston, 2000), the brain is assumed as a large ensemble of coupled nonlinear subsystems with labile and unstable dynamics. Nonlinear analyses of coupling provides an alternative approach to linear coherence methods with the important advantages of avoiding the conduction effect, limitation at defined frequencies and the impossibility of detecting the direction of the driving flow (Schanze & Eckhorn, 1997). Furthermore, real neuronal systems show out nonlinear input and output. A certain level of synchronization in various bands is needed in order to attain normal neuronal activity in physiological condition, whereas an excessive degree of synchrony can result in a pathological state such as epilepsy. Various nonlinear analysis approaches (e.g. Lenhertz & Elger, 1998; Le van Quyen *et al*. 2001; Palus *et al*. 2001) reflecting changes of synchrony have been successfully applied in anticipating epileptic seizures.

Since Bablyonatz's study (Bablyonatz & Salazar, 1985), nonlinear EEG analyses have been broadly used in sleep research. A progressive decrease of complexity from wakefulness to deep NREM sleep has been consistently reported (e.g. Fell *et al*. 1996; Kobayashi *et al*.1999). Terry *et al*. (2004) revealed significant age-dependent changes in NREM sleep in adult subjects. Janjarasjitt *et al*. (2008) described an increase of dimension complexity of neonatal sleep EEG with the neurodevelopment. There is growing evidence that people with autism spectrum disorder frequently exhibit atypical sleep architecture and suffer from sleep disorders (Richdale,

1999; Honomichl *et al*. 2002; Bruni e al. 2007). A reduced proportion of NREM 2, NREM 3 and NREM 4 stages has been described by several authors.

The aim of the study was to investigate the sensitivity of two-channel nonlinear "coarse-grained entropy information" analysis (CEI) (Palus *et al*. 2001) to night sleep EEG recording in young individuals with autism spectrum disorders. We asked the following question:

What are the differences in EEG brain dynamics during NREM sleep in terms of synchronization between patients with ASD and a control group? We hypothesized that ASD subjects would show a lower degree of synchronization with regards to the underconnectivity and reported NREM sleep abnormalities.

Table 1. EEG characteristics in patients with epileptiform abnormalities

AUTISTIC GROUP

Patient	Localization	Type of EEG abnormality
A 1	CPO bilat	rhytmical irregular high voltage sharp S,W
A 2	F bilat	sharp slow W
A 3	TO dx	biphasic sharp W
A 4	F bilat	low-voltage sharp W
A 5	FC bilat	S; episodes of SW complexes
A 6	F bilat	SW
A 7	FC sin	high-voltage S; W
A 8	TO sin	biphasic sharp W
A 9	C bilat	high voltage sharp W
A 10	CPT bilat	S; sharp W
A 11	F bilat	SW
A 12	CT dx	multiple spikes and SW complexes
A 13	generalized	SW complexes
A 14	generalized	episodes of theta W
A 15	CP central	low-voltage sharp W
A 16	TPO bilat	sharp W
A 17	multifocal with O sin and F dx max	biphasic sharp W; slow W
A 18	P	sharp W

CONTROL GROUP

Patient	Localization	Type of EEG abnormality
B 1	T dx	biphasic sharp W
B 2	FTP sin	high-voltage sharp and slow W; low-voltage S
B 3	P sin	low-voltage sharp W

Legend: S – spike; **W** – wave; **F** – frontal; **C** – central; **T** – temporal; **P** – parietal; **O** – occipital; **dx** – right; **sin** – left; **bilat** – bilateral

MATERIALS AND METHODS

1. Subjects

We examined a group of 27 patients diagnosed according to ICD-10 criteria in the spectrum of pervasive developmental disorders (childhood autism n=18; atypical autism n=5; Asperser's syndrome n=3; other childhood disintegrative disorder n=1), with the total mean CARS (Childhood Autism Rating Scale; Schopler *et al*. 1980) score of 36.0 (SD 5.0) pts. The mean age of the sample was 7.1 (SD 3.6) years. Fourteen of the patients (54 %) were mentally retarded. Their mean intellectual level was in the field of mild mental retardation; Stanford-Binet Intelligence scale 4th Edition for older children and Gessel Developmental Scales for youngest children were used. MRI scanning proved that no patient had a gross structural CNS abnormality. Four patients (15%) had a history of epileptic seizures (1x myoclonic seizures; 1x infantile spasms; 1x generalized seizures and 1x partial simplex seizures), fully compensated in the long term. Only one of the patients with a history of seizures was being treated with anti-epileptic medication (valproic acid 600mg per day) at the time of the examination.

The control group consisted of 20 non-autistic children (mean age of 8.4, SD 2.3 years) investigated within the frame of the research program for cochlear implantation. All control subjects had normal neurological examination. They suffered from perceptive deafness and had cochlear implants. Ten of them suffered from a mild form of developmental dysphasia. They were mentally non-retarded, with a mean of normal intellectual levels (evaluated by the Leiter International Performance Scale-Revised). None of the control subjects had a history of seizures.

2. EEG recordings

Overnight sleep video-EEG recording were undertaken in all subjects in the autistic and the control group, after one or two adaptation nights in the case of the autistic patients.

Twenty-one-channel EEG sleep recording was performed on Schwartzer EPAS Video/Audio and Schwartzer EPAS 32 Portable devices with BrainLab software. Scalp electrodes were placed according to the 10/20 international system. The EEG signal was processed from a referential montage, sampled at 200 Hz using an analogue to digital converter with 16 bit resolution; high-pass filtering was set at 0.5 Hz, low pass filtering was set at 70 Hz. The EEG recordings were evaluated by one experienced neurologist specializing in this field. Artefact episodes were excluded by visual examination. We included sleep stages NREM 2, NREM 3 and NREM 4 in the study. The mean length of the analyzed NREM sleep segment was 62 minutes in the autistic group and 63 minutes in the control group. In the autistic group, normal EEG was found in 9 patients (33%), epileptiform EEG in 18 patients (67%). In the

control group, normal EEG was found in 17 patients (85%), epileptiform EEG in 3 patients (15%). The EEG characteristics of the autistic and control subjects with epileptiform abnormalities are summarized in Table 1.

3. EEG analysis procedure

For the theoretical mathematical background and definitions of applied nonlinear analysis in this study, we refer to the work of Palus (Palus *et al*. 2001). We applied two methods of nonlinear analysis implemented in the proprietary software system "MESAN" (Motol EEG System Analyses). The first, the *Coarse-grained Entropy Rate (CER),* is a measure of the "chaoticity" or "complexity" and provides the same classification of states of chaotic systems as Lyapunov exponents and Kolmogorov-Sinai entropy. The CER characterizes the dynamics of individual signals and does not provide information about their mutual dynamic relations.

The second measure, *Coarse-grained Entropy Information (CEI),* reflects general dynamical interactions between two signals, being therefore appropriate for the investigation of the synchronization processes. It expresses the degree of synchronization (or coupling) between two signals; it is a measure of mutual information. CEI is identical to the "mutual coarse-grained information rate" (MCIR) created by Palus (Palus *et al*. 2001).

We have analyzed the data from the reference montage from 10 channels (F3, F4, F7, F8, C3, C4, T3, T4, P3, and P4) using the window length of 4096 samples, with an overlap of 75%, and 8 marginal equiquantal bins. For calculating analyses results, we have used data from 11 pairs (F3F4, C3C4, P3P4, F3F7, F4F8, C3T3, C4T4, F3C3, C3P3, F4C4, and C4P4).

RESULTS

1. Comparison of the autistic group and the control group

Statistically significant differences between the autistic and the control group were found using the ANCOVA in CEI analyses. Significant results within the three observed NREM stages are presented in Table 2.

The autistic group showed significantly *lower synchronization* in all three observed NREM stages. Maximal differences were found in the NREM 3 stage. A significantly *lower degree of synchronization in the autistic group* appeared during the NREM 2 phase for electrode pair C3C4. During the NREM 3 phase, lower synchronization in autistic patients occurred in 6 electrode pairs (F3F4, P3P4, C3P3, C4P4, C3C4, C4T4) and during NREM 4 in 2 electrode pairs (F3F4, C3C4). Lower synchronization was present in C3C4 through all NREM 2–4 stages.

No significant differences in mean values between the autistic and the control group in CER analysis were found using the ANCOVA method.

DISCUSSION

To our knowledge, our study is the first application of nonlinear analysis to quantifying EEG characteristics in patients with autism spectrum disorder. Therefore, the study results should be interpreted cautiously.

From a methodological point of view, the data analysis set up used proved the sensibility of CEI analysis to reveal clinically relevant differences in synchronization between the autistic and the control group. An important foundation for the internal consistency of results in CEI analysis is the absence of significant differences in mean values between the autistic and the control group

Table 2. Synchronization in electrode couples in the autistic group and the control group during sleep phases NREM 2, 3 and 4.

sleep phase	electrode couples	autistic group (n=27)		control group (n=20)		ANCOVA
		m	SD	**m**	SD	p
NREM2	**C3C4**	**.0281**	.0045	**.0304**	.0032	*
NREM3	**F3F4**	**.0616**	.0202	**.0692**	.0161	*** ⊗
	P3P4	**.0446**	.0111	**.0542**	.0144	*
	C3P3	**.0449**	.0097	**.0508**	.0081	*
	C4P4	**.0433**	.0089	**.0495**	.0111	*
	C3C4	**.0379**	.0084	**.0422**	.0047	*
	C4T4	**.0409**	.0073	**.0431**	.0057	*
NREM4	**F3F4**	**.0737**	.0211	**.0778**	.0189	**
	C3C4	**.0408**	.0067	**.0443**	.0051	*

Synchronicity values for electrode couples cf. section Methods. ANCOVA: Group differences considering age and IQ as covariates. Significant differences only are reported, significance levels:
* p<0.05; ** p<0.01; *** p<0.001, ⊗ p<0.05 with Bonferroni correction for 33 simultaneous tests.

in CER analysis using the analysis of covariance. Such possible differences in CER analysis would namely bias the results in CEI analysis.

We did not have a healthy reference group at our disposal. Our control group consisted of deaf children, half of whom had a mild form of dysphasia. The only study of nonlinear EEG dynamics in deaf subjects was carried out by Micheloyannis (Micheloyannis *et al*. 1998) who found in them a lower predictability in resting condition and more diffused cortical activation during reading. With regard to the higher proportion of white matter in the brains of both patients with developmental dysphasia and those with autism (Herbert *et al*. 2004), one could expect more significant differences than when comparing the autistic group to healthy control subjects.

We did not find significant differences between the two autistic subgroups with normal and epileptiform EEG. Looking for an explanation for this negative finding, we refer to the EEG characteristics of our sample. None of the autistic patients had continual epileptiform discharges of an electrical status epilepticus character during slow-wave sleep (ESES). Only two patients had generalized discharges. In agreement with Muñoz-Yunta *et al*. (2007), we observed common specific EEG abnormalities of various frequencies in the majority of them.

The crucial finding of this study is a lower degree of synchronization in the autistic group in comparison to control subjects during all three NREM stages with maximum difference in the NREM 3 stage. In a recent study of cortical connectivity using linear EEG analysis of coherence, Murias *et al*. (2007), found locally elevated coherence within the left hemisphere frontal and temporal regions in the theta (3–6 Hz) frequency range. In the lower alpha range (8–10 Hz), globally reduced coherence was evident in the ASD group within the frontal regions.

It is very tentative to refer our results to the altered connectivity in autism spectrum disorders. A part of interhemispheral connectivity is mediated by the corpus callosum. The thinning of the corpus callosum appears to be a specific morphological finding for ASD (e.g. Piven *et al*. 1997; Hardan *et al*. 2000; Waiter *et al*. 2005; Vidal *et al*. 2006). In our study, the difference between the autistic and the control group was most consistent in frontal and central areas.

The lower degree of synchronization in the autism group during NREM sleep corresponds also to the altered sleep patterns and architecture in autism (Richdale, 1999; Honomichl *et al*. 2002; Allik *et al*. 2006; Bruni *et al*. 2007). Limoges *et al*. (2005) revealed, according to other studies, increased duration of the NREM 1 stage, decreased proportion of NREM 2, NREM 3, and NREM 4 stages and fewer sleep spindles in persons with autism. A progress to deeper NREM stages is associated with an adequate level of synchronization. In this study, autistic patients showed a lower degree of synchronization during all three NREM stages with maximum intergroup difference in the NREM 3 stage.

The results of the presented study confirmed the general assumption of functional cortical underconnectivity in autism. The investigation of synchronization of processes in EEG provides a powerful tool for investigating underlying functional neurophysiological disturbances.

STATISTICS

The statistical analysis was performed using the Statistica software system. Due to different clinical characteristics of the autistic and the control group in the sense of the different mean age and intellectual level, we used the analysis of covariance (ANCOVA) for the comparison of mean values of synchronization of the autistic group with the control group with age and intellectual level as covariates in order to eliminate their influence. We compared mean CER values in the autistic and the control group by ANCOVA, because possible differences in CER analysis could bias the results in CEI analysis.

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