

Excess of High Frequency Electroencephalogram Oscillations in Boys with Autism

Elena V. Orekhova, Tatiana A. Stroganova, Gudrun Nygren, Marina M. Tsetlin, Irina N. Posikera, Christopher Gillberg, and Mikael Elam

Background: An elevated excitation/inhibition ratio has been suggested as one mechanism underpinning autism. An imbalance between cortical excitation and inhibition may manifest itself in electroencephalogram (EEG) abnormalities in the high frequency range. The aim of this study was to investigate whether beta and gamma range EEG abnormalities are characteristic for young boys with autism (BWA).

Methods: EEG was recorded during sustained visual attention in two independent samples of BWA from Moscow and Gothenburg, aged 3 to 8 years, and in age matched typically developing boys (TDB). High frequency EEG spectral power was analyzed.

Results: In both samples, BWA demonstrated a pathological increase of gamma (24.4–44.0 Hz) activity at the electrode locations distant from the sources of myogenic artefacts. In both samples, the amount of gamma activity correlated positively with degree of developmental delay in BWA.

Conclusions: The excess of high frequency oscillations may reflect imbalance in the excitation–inhibition homeostasis in the cortex. Given the important role of high frequency EEG rhythms for perceptual and cognitive processes, early and probably genetically determined abnormalities in the neuronal mechanisms generating high frequency EEG rhythms may contribute to development of the disorder. Further studies are needed to investigate the specificity of the findings for autism.

Key Words: Autism, beta, children, EEG, gamma, high frequency oscillations

High frequency (gamma) electroencephalogram (EEG) oscillations are intimately related to mental processes such as consciousness (Llinas and Ribary 1993), binding of sensory features into coherent percept (Engel and Singer 2001; Tallon-Baudry *et al.* 1996), object representation (Bertrand and Tallon-Baudry 2000), attention (Fell *et al.* 2003), and memory (Hermann *et al.* 2004; Lisman and Idiart 1995). Gamma oscillations can be subdivided into spontaneous, contributing to ongoing EEG, and stimulus related (steady-state, induced and evoked oscillations) (Galambos 1992), but these different classes of gamma oscillations may be generated in the same neural circuits (Basar 1980; Herrmann 2001).

High frequency rhythms (12–80 Hz) are generated in neuronal networks involving excitatory pyramidal cells and inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons (Whittington *et al.* 2000). Gamma oscillations (30–80 Hz) are enhanced with arousal and attention or by electrical stimulation of mesencephalic reticular formation (Rodriguez *et al.* 2004). Beta oscillations (12–30 Hz) include at least two classes of phenomena. One type of beta can be thought of as a slow gamma oscillation and can be caused by application of GABAergic drugs (e.g. barbiturates) or benzodiazepines. The other type of beta oscillations represents a sub-harmonic frequency of the underlying gamma. In this case interneurons continue to oscillate at gamma

frequencies, while excitatory neurons remain in relative refractoriness for a time greater than one period of interneuron gamma rhythm and fire only on a proportion of these periods.

The close relationship between fast EEG rhythms and cognitive processes make them an interesting topic in the field of biological psychiatry. Hermann and Demiralp (2005) summarized available data on gamma activity in different forms of psychopathology (e.g., epilepsy, attention deficit hyperactivity disorder [ADHD], schizophrenia, Alzheimer's disease) and concluded that disturbances in gamma synchronization mechanisms may contribute to many psychopathological symptoms. They related the lack of gamma-range EEG activity to the 'negative' psychiatric symptoms (e.g. progressive amnesia in Alzheimer's disease or typical negative symptoms of schizophrenia) and the excess of gamma activity to the 'positive' symptoms, such as hallucinations in schizophrenic patients and 'déjà vu' phenomena in epilepsy. In primary generalized epilepsy the gamma (30–100 Hz) spectral power in spontaneous interictal EEG exceeds that of healthy subjects 3 to 10 times (Willoughby *et al.* 2003b). The excess of fast oscillations in epilepsy may be related to abnormalities in GABAergic inhibitory systems (Schmitz *et al.* 2005) and/or in excitatory glutamatergic system (Hiscock *et al.* 2001; Pisa *et al.* 1980).

There is a high prevalence of epilepsy among individuals with autism (Gillberg and Billstedt 2000). Even in the absence of seizures the frequency of sleep EEG/magnetoencephalography (MEG) epileptiform abnormalities in autism is much higher than in general population (Baird *et al.* 2006; Chez *et al.* 2006; Lewine *et al.* 1999; Tuchman and Rapin 1997). These data suggest that increased fast frequency activity may be a characteristic EEG feature also in autism. Another indication of a possible relation between fast EEG activity and autism comes from recent data on genetically mediated abnormalities in GABAergic (Schmitz *et al.* 2005) and glutamatergic (Fatemi *et al.* 2002; Shuang *et al.* 2004) mediator systems in this disorder. The morphological integrity of GABAergic interneuron connections within cortical minicolumns is important for generation of normal gamma oscillations (Whittington *et al.* 2000). It is noteworthy, therefore, that the cortical

From the Department of Clinical Neurophysiology (EVO, ME), and the Department of Child and Adolescent Psychiatry (GN, CG), Sahlgrenska University Hospital, Gothenburg, Sweden; Moscow University of Psychology and Education (TAS, MMT, INP), Moscow, Russia.

Address reprint requests to Elena Orekhova, Ph.D., Department of Clinical Neurophysiology, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden; E-mail: elena@neuro.gu.se.

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minicolumns in autistic patients were shown to be more numerous, smaller and less compact than in controls, with reduced neuropil space in the periphery (Casanova *et al.* 2002). Casanova *et al.* (2003) suggested that such abnormal minicolumn organization may result in a deficit of inhibitory GABAergic fiber projections, which in turn may facilitate the occurrence of epilepsy in autism.

The data on fast EEG activity in autism are, however, scarce and controversial. Rossi *et al.* (1995) reported high proportion of 'fast activity' in EEG of patients with autism (3–31 years), especially in those with epilepsy or epileptiform EEG activity. However, they did not perform quantitative EEG analysis and the frequency of the 'fast activity' is unclear. Bashina and coauthors (1994) reported that beta (13.5–20 Hz) activity is increased in children with autism. On the other hand, Dawson *et al.* (1995) did not find increased power of fast activity (14–32 Hz) in children and adolescents with autism. Quantitative EEG studies in so-called 'psychotic children' have shown pathologically increased 13–33 Hz spectral power (Itil *et al.* 1976; Simeon and Itil 1975). Given that diagnostic criteria for autism were not established in the 1970s, the group of 'psychotic children' probably included those with autism spectrum disorders.

The presence of fast rhythms in EEG is usually considered as an electrophysiological index of cortical activation. Therefore, excess of beta and gamma rhythms in EEG of children with autism would support the hypothesis of abnormally high excitation/inhibition in cortical structures in this disorder (Rubenstein and Merzenich 2003).

In the present study we investigated ongoing high frequency EEG activity in young children with autism and age-matched typically developing children, testing the hypothesis that the amount of fast rhythms may be abnormally high in autism and that it may correlate with the severity of developmental disturbance in this disorder. EEG was obtained under a controlled condition of visual attention and behavioral stillness. To check reproducibility of results, we compared data obtained from two independent samples of subjects with autism from Moscow and Gothenburg. Given the absence of data on age dynamics of ongoing fast frequency activity during sustained visual attention in young children, its age-related changes in children also were analyzed. As high frequency EEG rhythms may depend on arousal (Gemignani *et al.* 2000) we controlled for autonomic arousal, roughly assessed by measuring heart rate (in the Gothenburg sample).

Methods and Materials

Participants

Participants were forty boys aged 3–8 years from Moscow ($n = 20$) and Gothenburg, ($n = 20$), diagnosed with autism ($n = 38$) or autism spectrum disorders ($n = 2$), and the same number of age-matched typically developing boys (TDB). The clinical groups will be addressed as 'boys with autism' (BWA). Information on experimental groups is summarized in Table 1.

The participants had no neurological disorders of known etiology (fragile-X, epilepsy, etc.). In the Gothenburg sample the diagnosis was based on DSM-IV-TR and ICD-10 criteria and confirmed by the Diagnostic Interview for Social and Communication disorders (DISCO-10; Wing *et al.* 2002). In Moscow sample, the diagnosis was set up by an experienced clinician, based on DSM-IV-TR criteria and confirmed by a clinical psychologist using the Childhood Autism Rating Scale (Schopler *et al.* 1986).

In the Gothenburg sample, the IQ/DQ level in BWA was assessed with Wechsler Preschool and Primary Scale of Intelligence-Revised (16 boys), Griffiths Mental Development Scale (3 boys) or Vineland Adaptive Behavioral Scale (1 boy) (Griffiths and Huntley 1996; Sparrow *et al.* 1984; Wechsler 1989). In the Moscow sample Kaufmann Assessment Battery for Children (9 boys) or Psychoeducational Profile (11 boys) were applied (Kaufman and Kaufman 1983; Schopler *et al.* 1990). The developmental delay was recalculated based on Mental Age derived from IQ or DQ measures: % delay = $100 - (\text{Mental Age} \times 100 / \text{Chronological Age})$. Gothenburg BWA were significantly older than Moscow BWA ($F(1, 38) = 7.7402, p = .008$), but did not differ in developmental delay (Gothenburg: mean delay 26.7, SD = 19.1; Moscow: mean delay 20.2, SD = 24.1; $F(1, 38) = .89, p = .35$).

All children of the Moscovs' sample were medication-free for at least two weeks before EEG recording. One subject of the Gothenburg's sample was on medication with sertraline, another boy was on medication with risperidone and melatonin and the third boy had melatonin as the only medication.

Control TDB group was comprised from healthy boys attending regular schools or day care centers. According to parent reports, they had no behavioral or language problems. They were matched to BWA by age.

Data Recording and Processing

EEG recording was carried out in an electrically-shielded chamber in Moscow and in a nonshielded room in Gothenburg.

Table 1. Characteristics of the Experimental Groups

Sample	Gothenburg		Moscow	
	Autism, $n = 20$	Control, $n = 20$	Autism, $n = 20$	Control, $n = 20$
Diagnosis	Autism (18), atypical autism (1), Asperger syndrome (1)	Healthy	Autism (20)	Healthy
Age (years, months)	Mean = 5y,9m Range: 3y,7m–8y,9m SD = 17.3m	Mean = 5y,8m Range: 3y,9m–7y,10m SD = 15.3m	Mean = 4y,7m Range: 3y,1m–6y,7m SD = 13.0m	Mean = 4y,10m Range: 3y,0m–6y,10m SD = 14.4m
Mental Delay ^a (in % of chronological age)	Mean = 20.2 Range: –24.4–68.9 SD = 24.1		Mean = 26.7 Range: –11.1–60.3 SD = 19.1	
Handedness ^b	Right (17), Left (2), Ambidextrous (1)	Right (17), Left (2), Ambidextrous (1)	Right (18), Ambidextrous (2)	Right (18), Left (2)

^aMental delay is negative when mental age exceeds chronological age.

^bHandedness was assessed using a parental questionnaire including 12 questions about preferential hand usage during performance of skilled actions (drawing, eating, pointing, etc.). The child was rated as right- or left-handed if he used the corresponding hand for more than 66% of items.

EEG was recorded at 19 standard electrode positions (Fp1, Fp2, F7, F8, F3, F4, T7, T8, C3, C4, P7, P8, P3, P4, O1, O2, Fz, Cz, Pz). Electrooculograph (EOG) electrodes were placed above and below the left eye as well as at the outer canthi of both eyes. Linked earlobes served as reference. For the Moscow sample electrophysiological data were recorded using a SynAmps system (NeuroScan) with standard built-in .5 Hz high-pass filter and 50 Hz notch filter. In the Gothenburg sample the electrophysiological signals were amplified using a Schwarzer EEG headbox with .4 time constant and 70 Hz low-pass filter and posthoc digitally filtered with .5 Hz high pass (3dB edge frequency between .4 and .8 Hz) and 46–54 Hz notch filters (3dB edge frequencies at 38.4 and 63.6 Hz). EEG recordings in Gothenburg were performed in the presence of rather strong power line noise and the gently sloping filter served as a weighting function, decreasing relative contribution of frequencies closer to 50 Hz into derivate gamma1 and gamma2 bands.

Testing was conducted only when the child was in a calm and alert state. The experimental session was videotaped and video-records were stored on hard disk, synchronized with EEG and EOG. Experimental conditions included sustained visual attention attracted by: 1) soap bubbles presented by an experimenter at about 1.5 meters distance from the child; and 2) computer presentation of moving fish ('Aquatica' screen saver). Each type of stimuli was presented for about 2 minutes. The periods of artefact-free EEG included in analyses from conditions (1) and (2) were further counterbalanced between BWA and TDB. The video-records were used to analyze the child's behavior. Periods when the child was distracted, talked, displayed overt emotional reactions, performed gross body movements, hand or arm movements, or any stereotype movements were excluded from EEG analysis.

Data were digitized on-line at 500 Hz, visually inspected off-line for subtle motor artefacts and the artefact-contaminated epochs were rejected. Bipolar EOG channels were used for correction of ocular artefacts with NeuroScan-4.3 software. In a few cases, when application of electrodes for vertical EOG recording was not possible due to poor cooperation of the child, manual rejection of the epochs containing ocular artefacts was performed. For all subjects at least 12 2.5-sec segments (mean = 36.6; SD = 15.1) of artefact-free EEG were analyzed. EEG data were fast Fourier transformed using a 2.5-sec window smoothed by Hanning weighting function and 50% overlap. Spectral power (SP) values were averaged across epochs to obtain average EEG spectra at 19 electrode locations. The mean SP was calculated in three high frequency bands: beta (13.2–24 Hz), gamma1 (24.4–44.0 Hz) and gamma2 (56.0–70 Hz). The SP values were log10 transformed to normalize the distribution.

The myogenic artefacts constitute a serious obstacle for investigation of scalp recorded spontaneous high frequency EEG oscillations (Goncharova *et al.* 2003). They may obscure real, or create artificial, differences in fast EEG activity between experimental groups. One should expect, however, that if the differences between BWA and TDB are due to the amount of myogenic artefacts, they should be pronounced at the electrodes positioned close to frontalis, temporalis and occipitalis muscles. If, on the other hand, between-group differences are more significant at less contaminated electrode locations, they most probably will reflect real between-group differences in high frequency EEG rhythms.

Statistical Analysis

The SP values were checked for normality using Shapiro-Wilks W-test, separately for the four experimental groups (Moscow/

autism, Moscow/control, Gothenburg/autism, Gothenburg/control). As the distributions often differed from normal, especially at the lateral electrode locations contaminated by myogenic artefacts, nonparametric Mann-Whitney U-test was used for between group comparisons of EEG SP values. Spearman rank order correlations were calculated to reveal age-related changes in fast frequency EEG power. Further analysis was restricted to the gamma1 SP at midline regions (Fz, Cz, Pz), where the variables' distributions did not differ from normal. The difference in age-related dynamics of gamma1 power in the experimental groups/samples was tested using Homogeneity-of-slopes model. The analysis was performed separately for each midline electrode position. The categorical factors were Sample (Moscow, Gothenburg) and Group (autism, control). Age was introduced as the continuous predictor. As no differences in slopes were found, we further applied the General Linear Model with only the main effects of Age. The other factors were repeated measures factor Electrode (Fz, Cz, Pz), and categorical factors Sample (Moscow, Gothenburg) and Group (autism, control).

To reveal the influence of developmental delay and emotional arousal on gamma1 SP, the regression analysis was performed separately for Moscow and Gothenburg experimental samples.

Results

The original EEG power spectra for all experimental groups are presented in Supplement 1. Figure 1 represents scalp distribution of the group mean log10 SP in beta, gamma1 and gamma2 bands in BWA and TDB and scalp topography of significant difference between the groups. As expected, power maxima of fast oscillations were observed at prefrontal, temporal or occipital regions, apparently due to a high contribution of myogenic artefacts at these electrode locations. The lowest beta and gamma SP values were observed at the midline, central and parietal regions, suggesting lower contribution of myogenic activity.

Results of Mann-Whitney U-test showed that in both samples, BWA had more high frequency rhythms at the midline, central and parietal regions, i.e. at the regions least contaminated by myogenic artefacts. In the Gothenburg sample, the difference was significant for the gamma1 band and marginally significant ($p = .05$) also at Fz for the beta band. In the Moscow sample, the between-group differences were generally of higher significance and were observed in beta, gamma1 and gamma2 bands. As differences between BWA and TDB were reproduced in both Moscow and Gothenburg samples for the gamma1, further analysis was restricted to this frequency band.

To study age-related dynamics of gamma1-range oscillations, Spearman correlations between age and gamma1 SP at each electrode position were calculated. Similar to our prediction of between-group differences, we expected that if an age-related trend of gamma1 band SP was primarily explained by myogenic artefacts, significant correlations with age would be greater in the vicinity of sources of these artefacts. The correlation coefficients are presented in Table 2. Significant ($p < .05$) negative correlations with age were observed in the Gothenburg TDB group for C3 and P3 electrode positions and in the Moscow TDB group for P7, P3, C4, P4, Fz and Cz electrode positions, relatively distant from the head muscles. There were no significant correlations between age and gamma1 SP in BWA with the only exception of that for T7 electrode position in the Moscow BWA group. To minimize the contribution of myogenic artefacts, we restricted further analysis to the least contaminated midline regions (Fz, Cz, Pz).

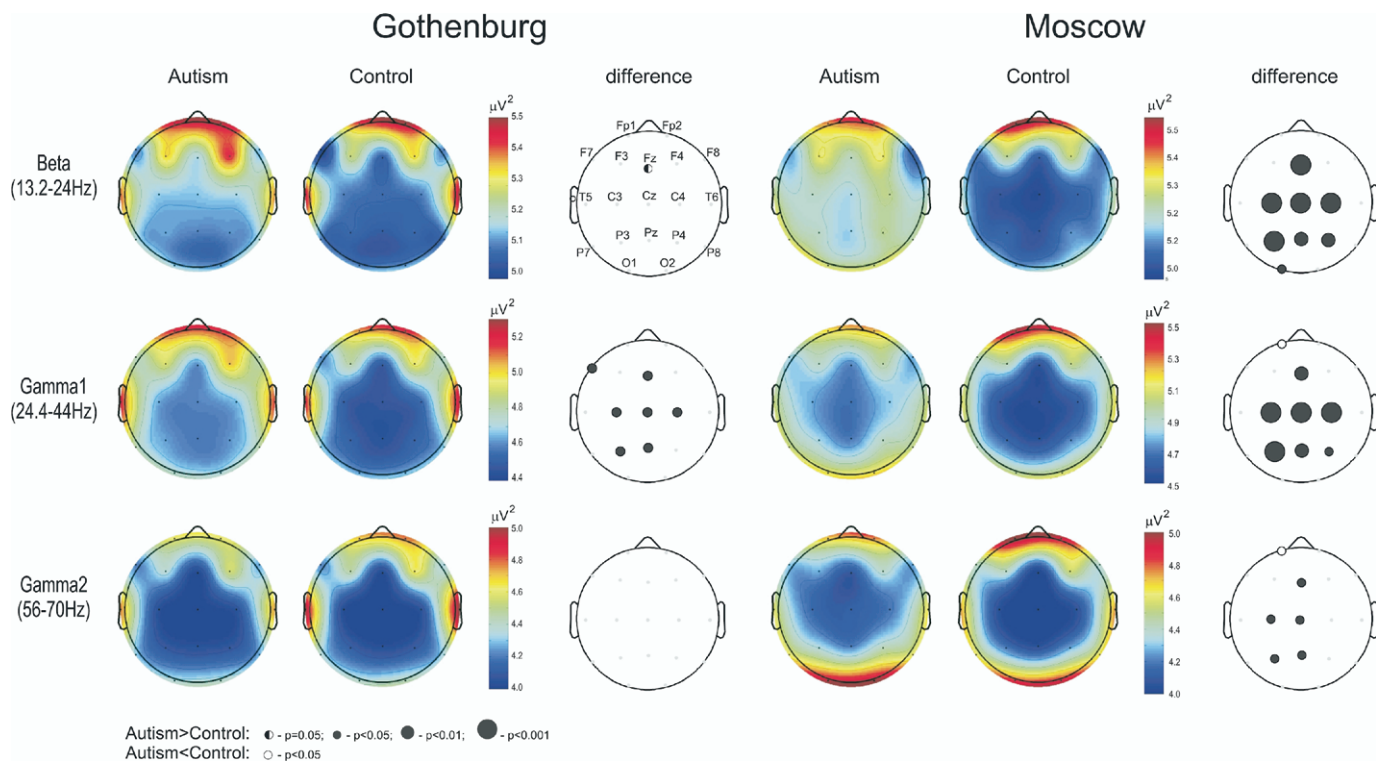


Figure 1. Grand average topographical maps of log10 spectral power of high frequency activity in boys with autism and typically developing boys and scalp distribution of between-group differences (Mann-Whitney U-test). High spectral power at prefrontal, mid-temporal and occipital electrode positions is explained by strong contribution of miogenic artifacts. Boys with autism have significantly higher spectral power at the electrode positions distant from the sources of miogenic artefacts.

The analysis of variance that included factors Sample (Moscow, Gothenburg), Group (autism, control), Electrode (Fz, Cz, Pz), and Age revealed significant age effect ($F(1,75) = 6.14, p =$

Table 2. Spearman Rank Order Correlations between Gamma1 Spectral Power and Chronological Age in Boys with Autism and Typically Developing Boys

	Gothenburg		Moscow	
	Autism (n = 20)	Control (n = 20)	Autism (n = 20)	Control (n = 20)
Fp1	-.26	-.20	.09	-.13
F7	-.40	-.04	.38	-.04
F3	-.42	-.24	-.05	-.27
T7	.22	-.03	.27	-.12
C3	-.33	-.45 ^a	-.07	-.38
P7	-.07	.03	.21	-.59 ^a
P3	-.33	-.45 ^a	-.22	-.45 ^a
O1	.10	.04	-.11	-.08
Fp2	-.38	-.18	.17	-.34
F8	-.27	-.17	.17	-.29
F4	-.16	.02	.10	-.40
T8	-.35	.12	.53 ^a	-.06
C4	-.28	-.34	.02	-.56 ^a
P8	-.26	.04	.32	-.36
P4	-.29	-.36	-.08	-.46 ^a
O2	-.03	-.12	-.05	.12
Fz	-.16	-.23	-.02	-.46 ^a
Cz	-.38	-.20	-.00	-.45 ^a
Pz	-.39	-.43	-.12	-.31

^a $p < .05$.

.02), due to an age-dependent decrease of midline gamma1 SP during sustained visual attention. There was also a highly significant main effect for Group ($F(1,75) = 20.93, p < .0001$), indicating higher midline gamma1 SP in BWA. There were no significant main or interaction effects for Electrode. The main effect for Sample (Moscow vs. Gothenburg) was marginally significant ($F(1,75) = 3.84, p = .054$), at least partly due to the different filtration techniques applied in Moscow and Gothenburg (see Supplement 1).

With highly significant differences in midline gamma1 SP between BWA and TDB, we expected that the amount of gamma1 activity may be closely related to severity of cognitive disturbance in the autistic disorder. To test this hypothesis, a regression analysis was performed separately for both BWA groups with percent of developmental delay and age as prediction variables and gamma power as a dependent variable. For a few children with IQ equal or higher than 100 the developmental delay was set at zero. The results of the analysis are summarized in Table 3 (1st and 2nd rows). There was a significant correlation of gamma1 SP with the degree of developmental delay in both Moscow (Cz) and Gothenburg (Fz, Cz) samples. Figure 2 shows the correlation between gamma1 SP and percent of developmental delay in BWA in Moscow and Gothenburg samples. In both samples, more delayed children had greater amounts of gamma1 EEG activity.

The differences in high frequency EEG power between BWA and TDB, as well as the positive correlation between gamma1 SP and developmental delay, could be influenced by between-subject differences in autonomic arousal. To gauge the level of autonomic arousal in BWA and TDB, we compared their mean R-R intervals measured during EEG registration in the Gothen-

Table 3. Dependence of Gamma1 Spectral Power on Age, Developmental Delay, and R-R Interval in Boys with Autism: Results of Regression Analysis

Sample	Predictors	Gamma1 Spectral Power (dependent variable)		
		Fz	Cz	Pz
Moscow	Age, Delay	$R^2 = .15$	$R^2 = .31$	$R^2 = .14$
		$F(2,17) = 1.55, ns$	$F(2,17) = 3.78^b$	$F(2,17) = 1.37, ns$
		Age, Delay Delay: ns	Age: ns Delay: $T = 2.70^b$	Age: ns Delay: ns
Gothenburg	Age, Delay	$R^2 = .30$	$R^2 = .30$	$R^2 = .19$
		$F(2,17) = 3.70^b$	$F(2,17) = 3.69^b$	$F(2,17) = 2.02, ns$
		Age: ns Delay: $T = 2.62^b$	Age: ns Delay: $T = 2.03^c$	Age: ns Delay: ns
	Age, Delay, R-R int.	$R^2 = .44$	$R^2 = .53$	$R^2 = .48$
		$F(3,16) = 4.23^b$	$F(3,16) = 6.00^a$	$F(3,16) = 4.97^b$
		Age: ns Delay: $T = 3.32^a$ R-R int.: $T = -1.99^c$	Age: ns Delay: $T = 3.14^a$ R-R int.: $T = -2.78^b$	Age: ns Delay: $T = 2.04^c$ R-R int.: $T = -3.00^a$

R^2 reflects the amount of variance explained by predictors in the regression equation.

^a $p < .01$.

^b $p < .05$.

^c $p = .06$.

burg sample. Although the BWA had slightly shorter mean R-R intervals (higher heart rate), the difference between groups was not significant ($F(1, 38) = .75, p = .39$). Subsequently, we included the mean R-R interval as a third predictor in the regression equation with the gamma1 SP as a dependent variable. The predicted negative correlation between gamma1 power and the mean R-R interval reached significance level at Cz and Pz electrode locations (Table 3, row 3), suggesting greater amount of high frequency activity in high autonomic arousal. However, the control for the mean R-R interval even increased correlation between gamma1 power and developmental delay, suggesting that developmental delay in BWA accounted for a part of interindividual variation in gamma1 SP independently of arousal level.

Discussion

The main findings of this study are 1) a pathological enhancement of spontaneous high frequency EEG oscillations in BWA, and 2) the relation of this enhancement to the degree of developmental disturbance. Both of these findings were reproduced for the two independent samples of subjects.

The difference in amount of fast frequency rhythms between BWA and TDB is unlikely to be explained by myogenic artefacts, because the majority of significant between-group differences were observed at electrode positions distant from the main sources of such artefacts. Furthermore, the distribution of significant between-group differences in the gamma1 band was similar for the two experimental samples (Figure 1).

A between-group difference in the level of autonomic arousal assessed via mean R-R interval is unlikely to account for the abnormally high amount of fast EEG rhythms in BWA or for its relation to the degree of developmental disturbance. In the BWA from the Gothenburg sample, controlling for the mean R-R intervals increases the correlation between gamma power and developmental delay (Table 3).

Between-group differences in behavioral and attentional conditions of EEG registration are unlikely to be a source of observed EEG differences, because we carefully controlled for

the presence of visual attention and behavioral stillness in all subjects. These considerations suggest that the elevated level of fast EEG rhythms in BWA could be a trait directly related to the pathophysiology of the disorder.

Although the abnormal increase of fast EEG rhythms in autism represents a robust phenomenon, there were differences between the two experimental samples. In the Moscow BWA sample, increased power was observed within beta, gamma1 and gamma2 frequency bands, whereas in the Gothenburg sample significant differences were limited to the gamma1 range. The difference in frequency range and reliability of the effect in the two patient samples may be related to the different age of the subjects (children in the Moscow sample were on average one year younger), and to the technical differences. In the Moscow sample, EEG was recorded in an electrically isolated chamber, while in the Gothenburg sample the recording was performed in an electrically unshielded room, resulting in a higher level of environmental electromagnetic noise.

The relation of the excess of high frequency EEG oscillations to the degree of developmental disturbance in BWA suggests that gamma generating abnormalities may be important for the pathophysiology of autism. This observation agrees well with data on significantly higher prevalence of epilepsy in the more impaired range of the autism spectrum (Gabis *et al.* 2005). It would be therefore important to further investigate whether the dynamics of fast EEG oscillations correlate with clinical improvement/efficacy of interventions in young children with autism and whether this EEG parameter can be of clinical value. We should note, however, that the choice of the normal control group in the present study does not allow us to conclude whether or not the relation between gamma power and degree of mental retardation is specific for autism. Comparison of children with developmental delay with and without autism is needed to clarify this issue.

The increased amount of high frequency EEG rhythms in BWA may result from genetically mediated disturbances in GABAergic or glutamatergic mediator systems, which are critically important for the generation of this type of oscillations.

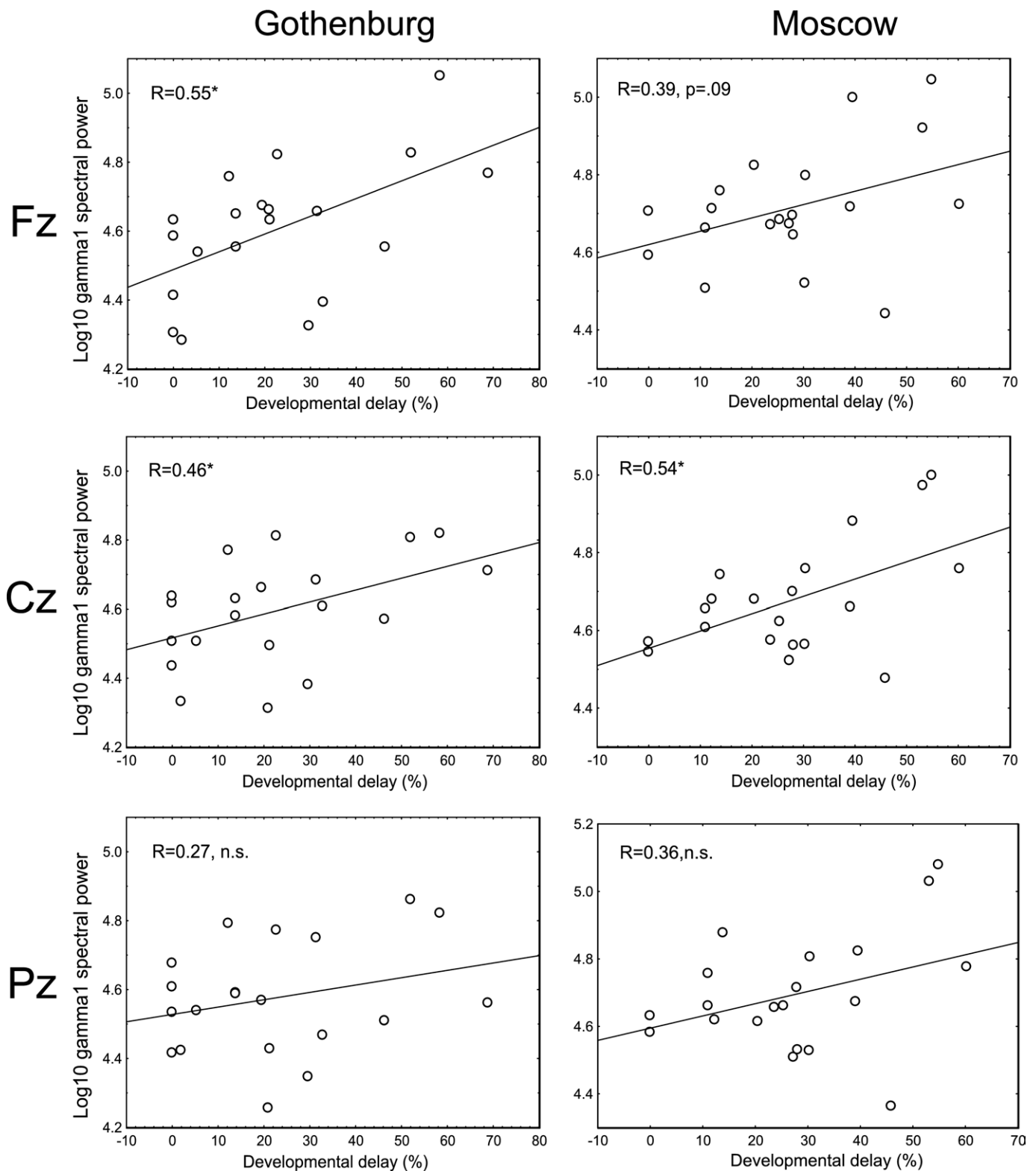


Figure 2. Correlation between gamma1 spectral power at midline regions and percent of developmental delay in children with autism. R values represent Pearson correlation coefficients.

Interestingly, a linkage and linkage disequilibrium has been found between high frequency (16.5–28 Hz) activity and a set of GABA receptor genes at chromosome 4 in normal subjects

(Porjesz *et al.* 2002) and the same loci were reported to be involved in autism (Ma *et al.* 2005). Hence, studies of high frequency EEG oscillations in individuals with autism may

appear useful to reveal genetically different subtypes of the disorder.

Our demonstration of increased spontaneous fast EEG oscillations in autism correspond well with the hypothesis of an elevated excitation/inhibition ratio in key neural systems involved in this disorder (Rubenstein and Merzenich 2003). Rubenstein and Merzenich suggested that an abnormally high excitability of cortical and subcortical structures in autism may result in formation of ‘noisy’ and unstable cortical networks. Such ‘noisy’ networks are expected to be poorly differentiated and susceptible to epilepsy.

The abnormally high level of spontaneous gamma in autism may lead to impaired ability of the noisy and unstable cortical networks to be effectively mobilized by sensory and cognitive processes. Indeed, induced gamma band response during face perception was reported to be lower in adults with autism (Grice *et al.* 2001). This interpretation is further supported by studies of spontaneous gamma oscillations in interictal EEG of patients with generalized epilepsy. These patients demonstrated both strongly increased baseline gamma level and its lower modulation by mental tasks (Willoughby *et al.* 2003a, 2003b).

The gamma1 spectral power of ongoing EEG recorded under visual attention condition decreased with age. This observation corresponds with data of Yordanova *et al.* (2002) who observed age related decrease of gamma power in ongoing EEG during auditory attention between 11 and 16 years of age. The finding of an age-related decrease in power of ongoing fast oscillations is consistent with the notion of greater localization and higher specialization of cortical processing with age (Casey *et al.* 2005; Durston and Casey 2006; Johnson 2001). High frequency oscillations are generated in more local cortical circuits than low frequency rhythms (von Stein and Sarnthein 2000) that explains their relatively low amplitude in scalp EEG records. More efficient and localized cortical processing during perceptually active state of sustained visual attention condition in the older children may be associated with narrowing of cortical distribution of ongoing gamma activities and, as a result, with lower amplitude of spontaneous scalp-recorded gamma oscillations.

Although the age-related gamma1 decrease was seemingly more pronounced in TDB than in BWA (Table 2), the difference in developmental trend of gamma1 SP between the two groups was not significant. One may still expect, however, that the age-related dynamics of high frequency oscillations in autism could be less evident due to the impact of developmental disturbance of gamma activity.

In the present study we recorded EEG in children under condition of visual attention characterized by high amount of miogenic activity that did not allow analysis of scalp distribution of fast EEG oscillations. The studies of other functional states (e.g. rapid eye movement sleep) would be helpful to provide information on state specificity (or nonspecificity) of the pathological excess of ongoing high frequency oscillations in autism and on their scalp topography. Taking into account the recent data on reduction in the power of the stimulus-locked gamma response in children with autism (Wilson *et al.* 2006) it would be also interesting to combine analysis of ongoing and stimulus-locked high frequency oscillations in the same subjects.

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Supplementary material cited in this article is available online.

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