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SHORT COMMUNICATION

Increased power of resting-state gamma oscillations in autism spectrum disorder detected by routine electroencephalography

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Abstract Experimental studies suggest that increased resting-state power of gamma oscillations is associated with autism spectrum disorder (ASD). To extend the clinical applicability of this finding, we retrospectively investigated routine electroencephalography (EEG) recordings of 19 patients with ASD and 19 age- and gender-matched controls. Relative resting-state condition gamma spectral power was variable, but on average significantly increased in children with ASD. This effect remained when excluding electrodes associated with myogenic gamma activity. These findings further indicate that increased resting-state gamma activity characterizes a subset of ASD and may also be detected by routine EEG as a clinically accessible and well-tolerated investigation.

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Introduction

Imbalances in cortical activity have been suggested to underlie the behavioral manifestations of ASD [1]. Ongoing neural activity can be assessed noninvasively during a resting-state EEG recording, i.e., in the absence of task performance or sensory stimulation, in which patterns of neural oscillations may be detected [2]. It has been suggested that elevated oscillatory activity in ASD might indicate hyperactivity in cortical circuits, and subsequently may be associated with the "autistic" state [3, 4], which is in agreement with a recent review summarizing EEG abnormalities during resting-state paradigms in ASD, reporting increased power in low (delta, theta) and high frequencies (beta, gamma) and reduced activity in middle-range frequencies (alpha) [2]. A few experimental studies report altered resting-state gamma activity by EEG or MEG. One EEG study has reported an increase in gamma activity during an eyes-open sustained attention task in children with ASD [5], while another found evidence for localized decreased gamma activity using the same EEG paradigm [6]. A recent MEG study found elevated 20–120 Hz activity during an eyes-closed condition predominantly in posterior brain regions [7].

As routine clinical EEG recordings are highly accessible and well tolerated for clinical diagnostics in young and mentally disabled children, the previous findings on gamma activity changes in ASD prompted us to analyze spectral content of eyes-closed resting-state in standard clinical EEGs in children with ASD and a control group. We hypothesized to find an increased gamma activity in

children with ASD that reflects the proposed imbalances in excitation and inhibition of neural activity.

Methods

Subjects

We retrospectively included children who were referred to the outpatient pediatric neurology department of the UMC Utrecht, between 2007 and 2013, with unexplained paroxysmal events. We distinguished two groups: children formally diagnosed with ASD and an age- and gender-matched control group. In the control group, a neurological or psychiatric disorder was excluded and all received normal education. In both the ASD as well as the normally developing group, epilepsy was excluded on basis of the medical history, follow-up of the paroxysmal events and EEG recording. The diagnosis of ASD was confirmed by a child and adolescent consultant psychiatrist [HB] and was made according to DSM IV guidelines. Intelligence levels were only available in a subset of the children with ASD. The institutional ethical committee approved the study and concluded that the Dutch Medical Research Involving Human Subjects Act did not apply, and written informed consent was not required.

EEG recordings

Routine EEG recordings were performed according to the international 10–20 system (SystemPlus Evolution, Micromed) against G2 as a reference electrode (placed between Cz and Fz) and referenced to an average montage for further analysis. Impedance of each electrode was kept below 5 kΩ. Data were high- and low-pass filtered at 0.008 and 70 Hz, respectively. Sampling frequency was 512 Hz. All EEG recordings contained 21 standard scalp electrodes. Electrodes Fp1, Fp2, A1 and A2 were left out of the analysis to minimize eye-induced movement and ECG artifacts. For each child, we visually selected four resting-state epochs (during an eyes-closed resting-state condition while subjects were awake) of each 8 s (each containing 4,096 samples) to ensure stable EEG characteristics [EvD] and independently re-inspected by a clinical epileptologist [FEJ]. There was no overlap between the selected epochs. Visual inspection was preferred over automatic approaches, since these may introduce complex new artifacts or biases [8].

Spectral analysis

The spectral power was obtained by converging the raw EEG recordings from the time domain into the frequency domain with a fast Fourier transformation with a frequency resolution of 1/8 s = 0.125 Hz. Calculations were performed using Brainwave software (available at http://home.kpn.nl/stam7883/brainave.html). The power was averaged for all channels, epochs and all subjects in the ASD and the control group separately. Considering the suggested association between increased gamma activity and ASD, we were primarily interested in the gamma frequency band (30–45 Hz) and run post hoc tests for the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz) and beta (13–30 Hz). Relative power was computed by dividing the fraction of each band divided by the sum of absolute power across 0.5–45 Hz.

Statistical analysis

Differences in relative spectral power, between the ASD and control group, were analyzed with a univariate analysis with age as covariate, as the residuals of the data were normally distributed. A p value of <0.05 was considered significant. Statistical analyses were performed in SPSS version 19.0.

Results

Patient characteristics

We included 19 patients with autism (mean age 10.6 ± 4.1 years, 16 boys) and 19 age- and gender-matched controls (mean age 10.1 ± 3.8 years, 16 boys). Clinical characteristics, including intellectual disability, psychiatric or neurological comorbidity and medication use are presented in Table 1. Intellectual disability was defined as IQ below 70 and was estimated on the basis of educational levels if quantitatively assessed intelligence quotients were absent. Intellectual disability was present in 8 out of 19 children in the ASD group. A minority of the children in the ASD group was on psychotropic medication (see Table 1). No psychotropic drugs were used by any of the controls.

Spectral analysis

The visual inspection showed that all selected epochs were free of interictal epileptiform discharges abnormal slowing, and electrocardiographic or motion-induced artifacts. The relative gamma power was significantly higher in the autistic group compared to the control group ($F = 10.679$, $p = 0.002$). There were no significant group differences for relative power in the other frequency bands. To explore the regional differences in the relative gamma frequency, we

Table 1 Patient characteristics

Nr.	Diagnosis	Axis I Comorbidity according to DSM IV criteria	ID	Medication during EEG
1	AD	None	Yes	None
2	AD	None	None	None
3	AD	None	Yes	None
4	AD	ADHD	None	None
5	AD	None	Yes	None
6	AD	ADHD	Yes	Methylphenidate, Risperidone
7	PDD NOS	None	Yes	None
8	PDD NOS	ADHD	Yes	None
9	PDD NOS	None	None	None
10	PDD NOS	ODD, Dysthymic disorder	Yes	None
11	PDD NOS	None	None	Olanzapine
12	PDD NOS	None	None	Aripiprazole
13	PDD NOS	None	None	None
14	PDD NOS	None	None	Pipamperone
15	PDD NOS	None	None	Risperidone
16	PDD NOS	None	None	Fluoxetine
17	PDD NOS	ADHD	Yes	Aripiprazole
18	PDD NOS	None	None	None
19	PDD NOS	None	None	None

M male, *F* female, *AD* autistic disorder, *PDD NOS* pervasive developmental disorder, not otherwise specified, *ADHD* attention-deficit hyperactive disorder, *ODD* oppositional defiant disorder, *ID* intellectual disability (refers to an IQ below 70

ran separate analysis for the occipital, frontal, temporal, parietal and central channels. A significantly higher gamma power was only found in the frontal, parietal and temporal channels. When excluding EEG channels commonly associated with myogenic artifacts (frontal, temporal and occipital), the significantly increased gamma frequency remained for the autistic group ($F = 8.506$, $p = 0.006$).

Discussion

This study found an average increase in relative gamma power in a cohort of children with ASD, detected by routine EEG recordings, as compared to an age- and gender-matched control group. Our findings are consistent with previous experimental findings in a MEG and EEG studies performed in a non-clinical setting [5, 7]. Routine EEG is a commonly available investigation and can be used without sedation across a wider range of age groups and in children with developmental disabilities. We noted that the distribution of gamma power was considerable in the ASD group and showed partial overlap with the control group. Our sample was unselected in terms of ASD subtype or cognitive capability, and the variability in gamma power may therefore reflect the widely acknowledged heterogeneous etiological nature of the disorder. Although the role of altered gamma activity in ASD is still under debate, it is suggested to relate to cognitive dysfunctions and may therefore offer an important entry to study neurophysiological correlates of autistic behavior [9]. It should be noted that altered gamma activity changes are not specific to ASD and have been related to alterations in common defects in GABAergic pathways observed across different developmental disorders such as schizophrenia and epilepsy [10].

Debate has centered on the question whether gamma activity can be measured reliably from EEG scalp recordings. Whitham and colleagues have suggested that frequency oscillations >20 Hz reflect myogenic artifacts [11]. Considering that our EEG epochs were carefully selected (i.e., free of myogenic artifacts), we believe that our results reflect an actual difference in gamma power between ASD and healthy controls, as was the case of several other studies investigating gamma activity in ASD [5, 12, 13]. Furthermore, when performing the analysis on the parietal and central electrodes only, electrodes less associated with myogenic artifacts, similar results were obtained. Together these arguments advocate for an actual differences in the gamma frequency band. We acknowledge that larger prospective controlled cohorts are needed to verify these findings considering the current debate on the value of gamma frequency band in EEG scalp recordings. Some methodological limitations need to be addressed. We had only limited information on the IQ level of patients. Although we did match our control group on age and gender, they were not IQ-matched which might have influenced group differences on spectral power of different frequency bands [14]. However, after exclusion of ASD patients with an intellectual disability, differences in gamma power remained significant. Further, medication use in the patient group could be accountable for altered spectral power in different frequency bands [15]. Again, after excluding ASD patients on medication, similar results were obtained. Clearly, the possible influences of IQ, use of medication, age and gender should be addressed in a larger study (with more statistical power). Possibly, these factors

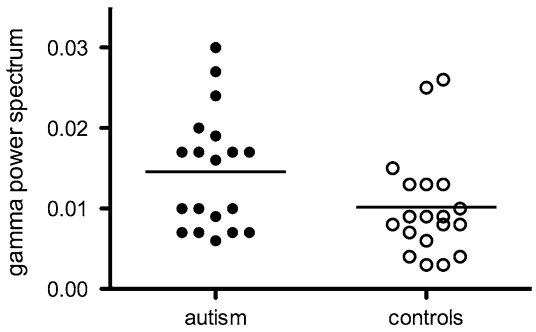

Fig. 1 Scatterplot relative gamma spectrum. In *black*, the distribution of the relative gamma power of the patients with autism spectrum disorder. In *white*, the distribution of the control group

might act as effect modifiers, explaining the considerable differences between individuals (Fig. 1).

In conclusion, this study shows that a subset of children with ASD may be characterized by abnormal gamma activity detected with eyes-closed resting-state EEGs. Future studies may relate resting-state examinations of routine EEGs to cognitive and behavioral profiles and test the hypothesis that gamma activity can be used to indicate defects in (sensory) information processing in ASD.

Conflict of interest The authors declare no conflict of interest.

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