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Magnetoencephalographic pattern of epileptiform activity in children with early-onset autism spectrum disorders

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Abstract

Objective: To provide further data around magnetoencephalographic (MEG) findings in early-onset autism spectrum disorders (ASD).
Methods: Thirty-six children (mean age 7 years) diagnosed of PDD (DSM-IV, ICD-10) were studied. There were 22 children with autistic disorder, 9 with Asperger's syndrome, and 5 with pervasive developmental disorder not otherwise specified (PDD-NOS). According to the Childhood Autism Rating Scale (CARS), the autistic disorder was mild to moderate in 11, and severe in 11. Neuroimaging studies using three-dimensional MRI as well as simultaneous MEG–EEG and fusion techniques through magnetic source imaging (MSI) were performed, with the aid of anesthesia in non-cooperative patients.
Results: Most patients had no EEG abnormalities. All ASD children showed common specific abnormalities in the shape of low amplitude monophasic and biphasic spikes (isolated or short bursts) as well as acute waves, predominantly distributed in the perisylvian areas. In Asperger's syndrome, epileptiform spikes were mostly found in the right hemisphere. No lateralized epileptiform activity was observed in non-Asperger's autistic patients.
Conclusions: MEG epileptiform activity is frequently documented in children with early-onset ASD.
Significance: Subclinical epileptiform activity is present especially in the perisylvian regions for many patients with ASD.

Keywords: Magnetoencephalography; Pervasive developmental disorders; Autistic spectrum disorders; Epileptiform activity pattern

1. Introduction

Pervasive developmental disorders (PDDs) refer to a group of conditions that involve severe distortions in the development of many basic psychological functions that are not normal for any stage of development. These distortions are manifested in sustained social impairment, speech abnormalities, and peculiar motor movements. Autistic spectrum disorder (ASD), a subtype of PDD, includes a continuum of conditions or behaviors unified by impairments in social interactions, communication and restricted behaviors or interests. The'triad' of impairments range in severity and may occur in varying combinations; and affected individuals extend from a wide range of intellectual

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abilities, from people with learning difficulties to those with above average intelligence. The common denominator for all of these disorders remains the significant and detrimental defect in socialization, almost invariably resulting in poor social adjustments, and inadequate or completely absent social interaction. Autistic disorder (autism) is an ASD characterized by the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interest. Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual. Asperger's syndrome is characterized by severe, sustained, clinically significant impairment of social interaction, and restricted repetitive and stereotyped patterns of behavior. In contrast to autism, there are no clinically significant delays in language or cognitive development. Language functioning includes superficially, perfect expressive language, formal pedantic language, odd prosody, peculiar voice characteristics, impairments of comprehension with misinterpretation of literal/implied meanings. Non-verbal communication problems are characterized by limited use of gestures, clumsy/gauche body language, and limited facial expressions in social interaction.

The category of pervasive development not otherwise specified (PDD-NOS) is used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and non-verbal communication skills, or when stereotyped behavior, interests, and activities are present, but the criteria are not met for a specific PDD.

Primary ASD, ranging from Asperger's syndrome to different levels of early infantile autism (low, moderate, severe), cryptogenetic ASD, and secondary ASD have been also considered from a neuropediatric standpoint (Muñoz Yunta et al., 2004).

Recently, epileptic seizures have been documented in 8–42% of patients with ASD (Tuchman and Rapin, 2002; Canitano et al., 2005; Hughes and Melyn, 2005; Kagan-Kushnir et al., 2005; Danielsson et al., 2005). However, the significance of epileptiform activity is controversial. Moreover, a clinical diagnosis of ASD cannot be confirmed by pathognomic electroencephalographic or polysomnographic features.

Magnetoencephalography (MEG) is a non-invasive method for identifying zones of abnormal brain electrophysiology, localizing and characterizing the electrical activity of the central nervous system by measuring the associated magnetic fields emanating from the brain. In children with autistic regressions, MEG showed significantly greater sensitivity to this epileptiform activity than simultaneous EEG, 1-h clinical EEG, and 24-h clinical EEG (Lewine et al., 1999). The experience with the use of MEG in autism is limited (Bailey et al., 2005; Kasai et al., 2005). This cross-sectional study was conducted to provide further data around MEG findings in autistic children.

2. Patients and methods

The study population consisted of a convenience sample of 36 non-consecutive children (mean age 7 years) with a tentative diagnosis of PDD who were referred to the Unit of Neuropediatrics of Hospital del Mar (Barcelona, Spain) for full evaluation and workup studies. The clinical diagnosis was made by a clinically experienced neurologist and a neuropsychologist using DSM-IV (American Psychiatric Association, 1994) and ICD-10 criteria (World Health Organization, 1992). Moreover, a research group of psychologists evaluated all patients diagnosed of ASD using the Childhood Autism Rating Scale (CARS) in order to classify patients into low-moderate and severe autism (Schopler et al., 1980). The CARS is a 15-item behavioral rating scale developed to identify children with autism, to distinguish them from developmentally handicapped children without the autism syndrome, and to differentiate among the levels of severity. Each of the 15 items is given a rating from 1 to 4 and after all 15 items have been rated, then the scores are summed. Scores below 30 are categorized as non-autistic and scores of 30 and above are categorized as autistic (mild-moderate 30–37; severe 38–60). In conjunction with CARS, the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989) and the Autism Diagnostic Interview-Revised (ADI-R) (Le Couteur et al., 1989; Lord et al., 1994) were administered for the establishment of a firm diagnosis of autism. The Australian Scale for Asperger's syndrome (ASAS) (Attwood, 1998), The Childhood Asperger Syndrome Test (CAST) (Scott et al., 2002) and the high-functioning Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers et al., 1999) were used for the diagnosis of Asperger's syndrome. Patients with regression history assessed by anamnesis were excluded.

There were 22 children with autistic disorder, 9 with Asperger's syndrome, and 5 with pervasive developmental disorder not otherwise specified (PDD-NOS). According to CARS, the autistic disorder was mild to moderate in 11, and severe in 11. Autism spectrum disorders (ASD) include all study groups except PDD-NOS ($n = 31$).

The study protocol was approved by the Institutional Review Board of the participating hospitals, and written consent was obtained from the parents or legal guardians of all autistic patients and controls who took part in the study.

2.1. Neuroimaging studies

MRI studies were performed before MEG using a superconductive 1.9 Tesla system (Prestige 2T, General Electric Medical Systems, Milwaukee, WI) with a head coil. A sagittal three-dimensional spoiled gradient-echo (SPGR) slab was positioned to include the entire head, and images were acquired with the following parameters: repetition time of 25 ms, echo time of 6 ms, flip angle 28°, field of view of 25×25 cm, matrix of 256×256, section thickness 1.1 mm with no interslice gap, and 1 NEX. The number of slices

varied between 110 and 120. Images acquired were stored in compact disc.

After a period no longer than 2 weeks, patients were studied using MEG technique. Magnetoencephalographic recordings were taken during wakefulness with the patient inside a magnetic shielded room, using a 148 channel whole-head MEG Magnes 2500 WH (4D NeuroImaging Technologies, Inc., San Diego, CA). A typical recording session requires the patient to place his/her head inside the magnetometer's helmet remaining immobile. Simultaneous EEG using the 10–20 international system, electrocardiogram (EKG) and electrooculogram (EOG) recordings were performed in all patients. EKG and EOG helped to detect artifacts (Lu et al., 1992). MEG studies in non-cooperative patients were performed under anesthesia. Three anesthetic protocols were randomly used. Type A included midazolam 1.5 mg/10 kg, ketamine 3 mg/kg and fentanyl 2 μg/kg; type B, fentanyl 2 μg/kg and droperidol 1 mg/kg; and type C, midazolam 0.3 mg/kg and propofol 1 mg/kg. During the recording, patients remained awake or under anesthesia, and no activation methods were used. Each recording session lasted 20 min and it was acquired using a 678.17 Hz sample rate and a 0.1–100 Hz band-pass filter. MEG and EEG data were digitized and filtered (1–70 Hz band-pass filter) for analysis. The signal analysis comprised visually selected segments of MEG and EEG which contained abnormal activity free from artifacts. The examiner was blind to the subject's clinical history.

An equivalent current simple dipole model (ECD) was used to calculate the spatial location of the neuronal currents responsible for the genesis of the abnormal activity (Gallen et al., 1995). ECD localization was calculated in regard to the Cartesian coordinates defined by the fiducial anatomic markers (bilateral preauricular points and nasion). The precise fixation of the Cartesian coordinates in the patient's MRI was carried out with the aid of the STAR program (Schwartz et al., 1999). Dipole selection criteria for sharp waves and spikes comprised a correlation coefficient greater than 0.95, a root mean square of at least 400 ft, a magnetic dipole moment under 400 nAm, a goodness of fit over 0.95 and a confidence volume under 15 cm^3 (Wheless et al., 1999). Equivalent current dipole was generally selected from a segment ranging from 20 ms before the spike or sharp wave onset to 20 ms after its maximum amplitude point. Usually more than one dipolar moment per spike was selected. The location of the magnetic dipoles corresponding to sharp waves and spikes in the recording was calculated (Amo et al., 2004). MEG results were expressed in dipoles per minute (d/min). The MEG areas studied are shown in Fig. 1.

The Mann–Whitney *U* test was used for the comparison of two groups of continuous data, and the Wilcoxon signed-rank test for paired samples of continuous data such as two loci in the same subject (e.g., intraperisylvian vs. extraperisylvian areas). Data were analyzed using SPSS for Windows (version 11.5; SPSS, Inc., Chicago, IL). A *P* value of 0.05 or less was considered statistically significant.

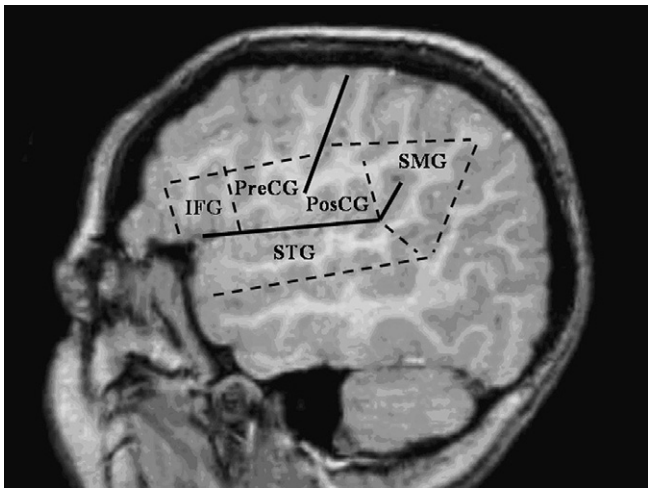

Fig. 1. Cerebral regions classified as Perisylvian areas. IFG (Inferior frontal gyrus), PreCG (Precentral gyrus), PosCG (Postcentral gyrus), SMG (Supramarginal gyrus) and STG (Superior temporal gyrus).

3. Results

Clinical data and individualized results of MEG studies for the 36 PDD children are shown in Table 1. In the EEG, no paroxysmal activity was detected in 35 (97.2%) of the 36 PDD children. In a 5-year-old boy with severe autism and history of epileptic seizures, biphasic temporal peak-waves were documented in the EEG.

MEG studies were performed under anesthesia in 28 (77.8%) autistic patients. There were no differences in MEG findings in relation to the anesthetic protocol used. From a morphological standpoint, two different types of MEG abnormalities were recorded: (a) low amplitude (<1 pT) monophasic or biphasic spikes of 10–70 ms duration, appearing as short bursts lasting approximately 1 s resembling paroxysmal rhythmic activity at 9 to 10 Hz; and (b) isolated monophasic or biphasic spikes (10–70 ms) and sharp waves (70–200 ms) with amplitude of 1–2 pT resembling epileptic spikes (Fig. 2). In the group of Asperger's syndrome a median of 1.45 d/min was recorded, in the group of low-moderate autism 1.29 d/min, and in the group of severe autism 0.70 d/min. However, in 5 (16.1%) of the 31 children with ASD, pathological activity was not registered (four of these patients had received anesthesia).

As shown in Table 2, there were only statistically significant differences between MEG activity in the intraperisylvian area compared with the extraperisylvian area in the groups of severe autism and ASD. Children with severe autism showed a median number of d/min of 0.6000 (25th–75th interquartile range 0–1.6500) in the intraperisylvian area compared with zero (range 0–0.2000) in the extraperisylvian area (Wilcoxon test, $P = 0.017$). On the other hand, the ASD group also manifested significantly higher activity in the intraperisylvian area (median 0.6000 d/min, range 0.2500–1.800) than in the extraperisylvian area (median 0.2000 d/min, range

Table 1
Characteristics and MEG results for individual patients

Sex	Age yr	Diagnosis	EEG	Anesthesia	CARS score	MEG (d/min)					
						Predominant activity	Total	Intraperisylvian activity			Extra perisylvian activity
								Left	Right	Total	
M	5	Asperger's syndrome	Normal	Type A	32.5	Right > left	18.6	0.6	9.3	9.9	8.7
M	10	Asperger's syndrome	Normal	No	30.5	Right > left	5.1	0	0	0	5.1
F	5	Asperger's syndrome	Normal	Type A	30	Right > left	3.7	0.9	1.8	2.7	1
M	5	Asperger's syndrome	Normal	No	30	Normal	0	0	0	0	0
M	11	Asperger's syndrome	Normal	Type C	32.5	Right	1.3	0.35	0.25	0.6	0.7
F	9	Asperger's syndrome	Normal	Type C	31	Normal	0	0	0	0	0
M	9	Asperger's syndrome	Normal	No	30	Right > left	1.45	0	0.6	0.6	0.85
M	14	Asperger's syndrome	Normal	No	29	Right > left	0.85	0.3	0.55	0.85	0
M	6	Asperger's syndrome	Normal	No	28	Right > left	1.45	0.35	0	0.35	1.1
M	6	Low-moderate autism	Normal	Type A	32.5	Left > right	5.8	1.9	1.2	3.1	2.7
M	9	Low-moderate autism	Normal	Type A	32.5	Right > left	4	0.3	2.8	3.1	0.9
M	7	Low-moderate autism	Normal	Type B	30.5	Left > right	0.55	0.45	0.05	0.5	0
M	4	Low-moderate autism	Normal	Type C	31	Left	1.68	0.9	0	0.9	0.05
M	5	Low-moderate autism	Normal	No	31	Right	0.4	0	0.4	0.4	0
M	4	Low-moderate autism	Normal	Type A	36	Right > left	10.3	0.7	7	7.7	0
M	8	Low-moderate autism	Normal	Type A	38	Right	2.7	0	2.1	2.1	0.6
M	4	Low-moderate autism	Normal	Type C	35.5	Right > left	2.4	1.1	0.7	1.8	0.6
F	7	Low-moderate autism	Normal	Type C	36.5	Left	0.9	0.5	0	0.5	0.4
M	6	Low-moderate autism	Normal	Type C	36	Right	0.75	0	0.35	0.35	0.85
F	9	Low-moderate autism	Normal	Type A	33.5	Right > left	0.3	0.1	0.2	0.3	8.7
M	4	Severe autism	Normal	Type A	49.5	Left > right	1.9	1.65	0	1.65	0.25
M	5	Severe autism	Abnormal[a]	Type A	49.5	Left > right	1.9	1.65	0	1.65	0.25
M	4	Severe autism	Normal	Type A	50.5	Right	0.8	0	0.8	0.8	0
M	4	Severe autism	Normal	Type A	45	Left > right	0.2	0	0	0	0.2
M	8	Severe autism	Normal	Type A	38.5	Right	0.6	0	0.6	0.6	0
F	12	Severe autism	Normal	Type A	38.5	Left	3	3	0	3	0
M	3	Severe autism	Normal	Type B	41.5	Normal	0	0	0	0	0
M	3	Severe autism	Normal	Type A	40	Right	1.3	0	1.3	1.3	0
M	4	Severe autism	Normal	Type C	42.5	Normal	0	0	0	0	0
M	4	Severe autism	Normal	Type C	39	Normal	0	0	0	0	0
M	2	Severe autism	Normal	Type C	41	Left	0.25	0.25	0	0.25	0
M	6	PDD-NOS	Normal	Type A	35	Right > left	4.6	0.7	0.65	1.35	3.25
F	16	PDD-NOS	Normal	No	17.5	Right > left	1.2	0.55	0.65	1.2	0
M	8	PDD-NOS	Normal	Type C	29	Left > right	1.35	0	0.55	0.55	0.8
M	8	PDD-NOS	Normal	No	26.5	Left > right	1.45	0	0.6	0.6	0.85
M	6	PDD-NOS	Normal	Type A	45	Right	7.5	0	0	0	7.5

Acute focal waves.

PDD-NOS, pervasive developmental disorder not otherwise specified.

[a] History of epileptic seizures. The EEG showed biphasic temporal peak-waves.

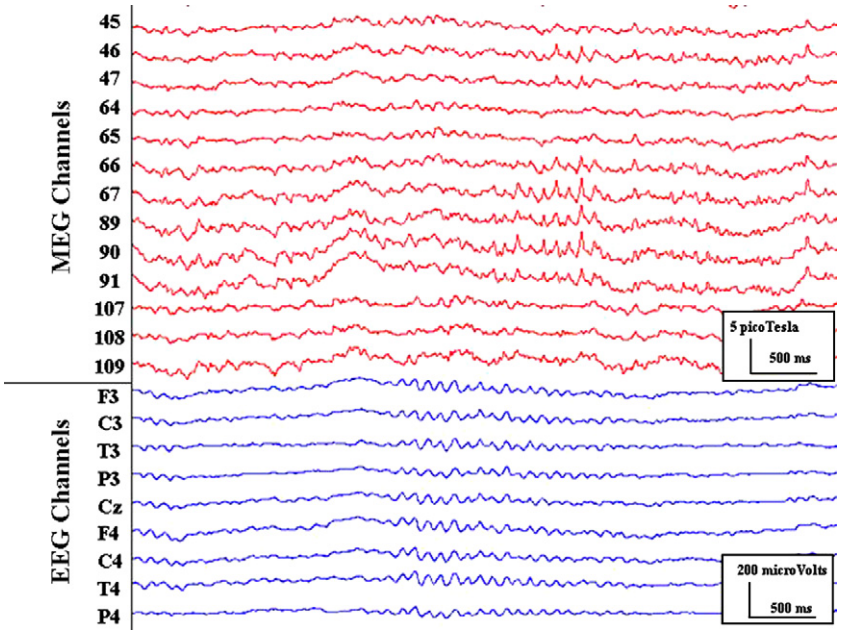

Fig. 2. MEG–EEG recording showing paroxysmal rhythmic activity at 9 Hz seen exclusively in the MEG tracing. MEG right fronto-temporal channels (upper tracing in red) and EEG channels monopolar montage with Cz as reference (lower tracing in blue).

0–0.8500) (Wilcoxon test, $P = 0.014$). All other comparisons were not statistically significant, including MEG activities in the intraperisylvian areas (Mann–Whitney U test, $P = 0.894$) and extraperisylvian areas (Mann–Whitney U test, $P = 0.161$) between the PDD-NOS and ASD groups.

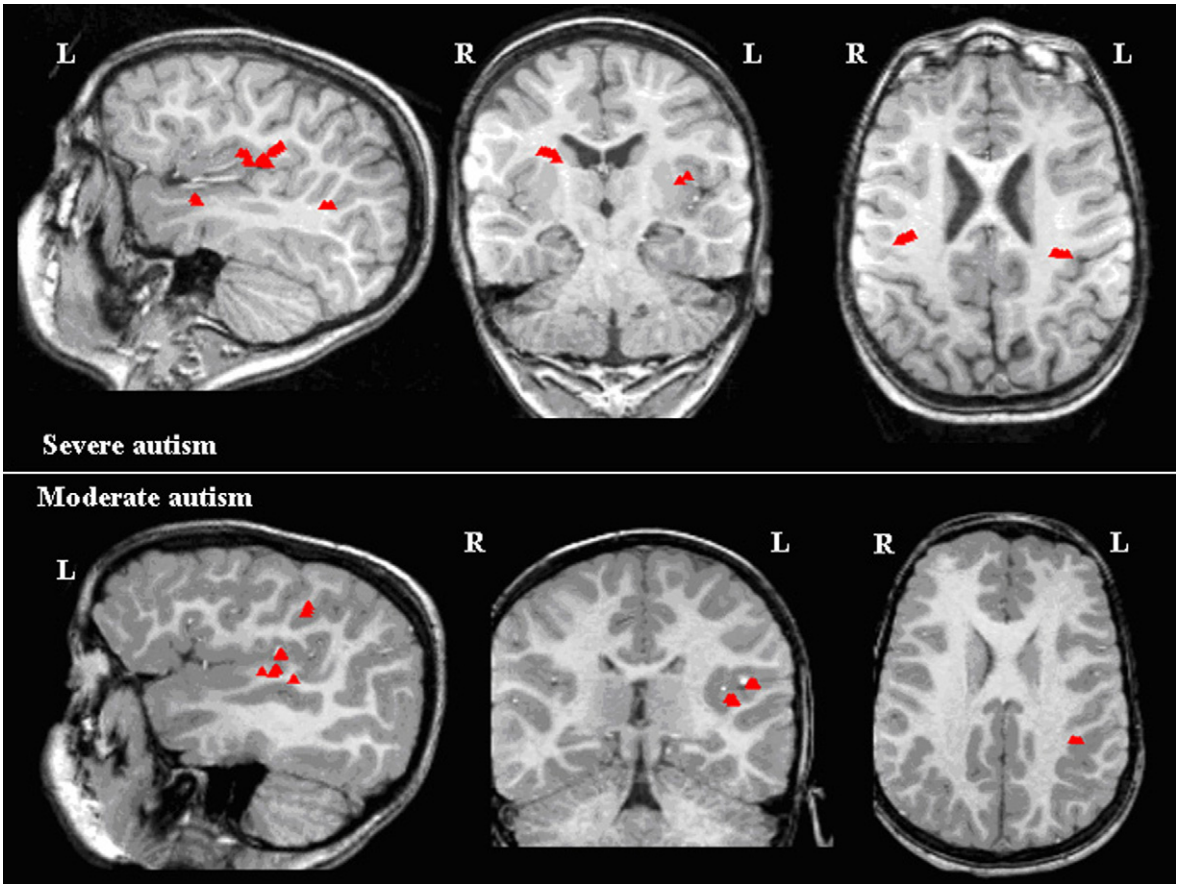

Fig. 3. Representation of MEG dipoles on MRI scans in a case of severe autism compared with moderate autism (triangles: paroxysmal rhythmic activity dipoles).

Table 2
MEG activity in the study population

Study group	Intraperisylvian area (d/min)		Extraperisylvian area (d/min)		*P* value[a]
	Median	25th–75th range	Median	25th–75th range	
Asperger's syndrome, $n = 9$	0.6000	0–1.775	0.8500	0–3.100	0.866
Low-moderate autism, $n = 11$	0.9000	0.4000–3.1000	0.6000	0–0.900	0.119
Severe autism, $n = 11$	0.6000	0–1.6500	0	0–0.2000	0.017
ASD, $n = 31$	0.6000	0.2500–1.8000	0.2000	0–0.8500	0.014
PDD-NOS, $n = 5$	0.6000	0.2750–1.2750	0.8500	0.4000–5.3750	0.223

ASD, Autism spectrum disorders (Asperger's syndrome and low-moderate and severe autism).
[a] Wilcoxon test.

Representation of MEG dipoles on MRI scans in a case of severe autism compared with moderate autism is shown in Fig. 3, and in a case of Asperger's syndrome compared with PDD-NOS is shown in Fig. 4.

As a result of the presence of epileptiform activity in all patients, treatment with lamotrigine was administered. In all cases, improvement of clinical manifestations of subclinical seizures and autistic behavior was observed.

4. Discussion

In the present study, MEG identified epileptiform activity in 86% of children with PDD, a percentage similar to that observed in the clinical series of 50 patients with ASDs reported by Lewine and colleagues (1999), in which MEG showed epileptiform activity in 82% of patients. In this respect, our study provides an important general replication of the prior study by Lewine et al. (1999) and adds evidence that subclinical epileptiform activity is present, particularly in the perisylvian regions, in many children with ASD. Data of both studies demonstrate the clinical value of MEG in characterizing these patients. All our ASD patients had a history of unusual behavior, such as blinking, covering ears with hands, sudden screaming, spinning and fixed look, etc., which may indicate a subclinical crisis (Muñoz Yunta et al., 2003).

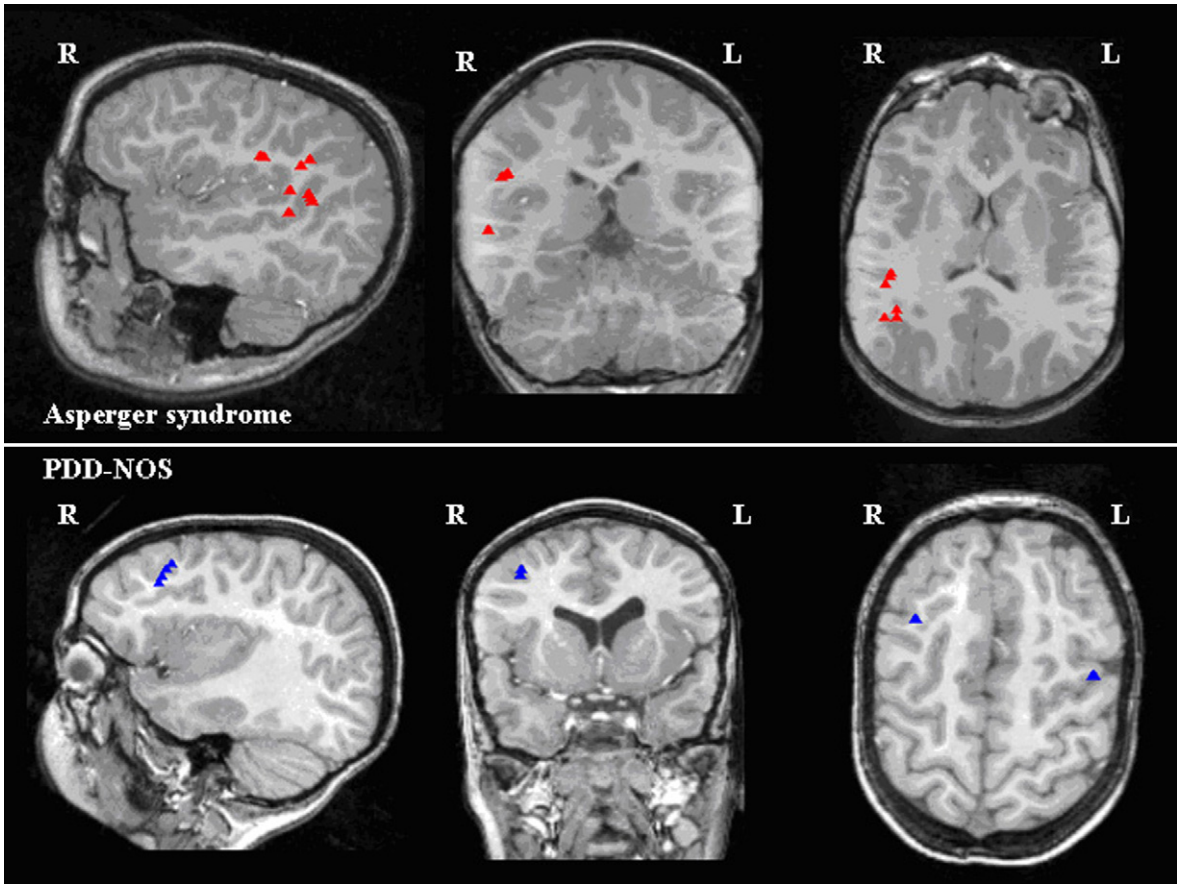

Fig. 4. Representation of MEG dipoles on MRI scans in a case of Asperger's syndrome compared with PDD-NOS (triangles: paroxysmal rhythmic activity dipoles).

MEG provides evidence for the important role of perisylvian areas in patients with ASD. Different MEG patterns between patients with Asperger's syndrome and the remaining autistic patients were observed. Patients with Asperger's disorder showed MEG activity predominantly in the right perisylvian area, whereas autistic children showed distribution between both perisylvian areas (right and left), with even a higher number of dipoles in the left hemisphere. We also found that in a patient not included in this study with Landau–Kleffner syndrome, MEG patterns showed focalized bilateral epileptiform activity in both perisylvian regions but more evident in the left perisylvian region, localized in the Wernicke area as already reported in 6 children with Landau–Kleffner syndrome in the study of Lewine et al. (1999) and in agreement with data of Sobel et al. (2000).

MEG data were compared with simultaneously recorded EEG data and only 1 child with severe autism showed alterations in the EEG. In the study of Lewine et al. (1999), simultaneous EEG revealed epileptiform activity in 68% of cases. This disparity in results between EEG and MEG is due to relatively small amplitude of paroxysmal rhythmic activity, generally less than 1 pT (for comparative purposes, the amplitude of a MEG epileptic spike ranges from 1 to 5 pT) (Hämäläinen et al., 1993). Since the magnetic fields are not distorted by the resistive properties of the skull, small potentials like these can be recorded. Small amplitude EEG signals, however, are easily attenuated by the non-homogeneous boundaries of the brain and skull, often escaping detection (Del Gratta et al., 2001). However, it should be noted that in our study, EEG was brief and prolonged EEG data in sleep were not assessed. The brief EEG may probably account for the lack of EEG abnormalities detected in the sample. On the other hand, the brief co-recording with the MEG especially in patients under anesthesia could have altered spike activity and decreased MEG activation as well.

Epileptiform abnormalities in different populations have been reported. In an electroencephalographic screening of 3225 non-epileptic psychiatric inpatients, epileptiform activity was detected in 2.6% of patients (Bridgers, 1987), and in a cohort of non-epileptic subjects in 2.2% (Zivin and Marsan, 1968). In patients with psychogenic non-epileptic seizures, EEG abnormalities were found in 12.3% of cases (Reuber et al., 2002). In healthy young subjects, the incidence of epileptiform potentials ranged from 0.5% to 2.4% (Gregory et al., 1993). In the present study, the number of MEG d/min was inversely related to the severity of the disorder, from a median of 1.45 d/min in patients with Asperger's syndrome to 1.29 d/min in low-moderate autism and 0.70 d/min in severe autism. It may be hypothesized that an evolutional dysmaturity process is being observed, so that the more severe the condition, the higher the number of spikes. These findings, however, should be interpreted taking into account that all severe autistic children were examined under anesthesia, whereas most of the cooperative Asperger patients were not.

On the other hand, it is known that some anesthetic regimens promote slow-wave sleep and may activate interictal activity. Modica et al. (1990) evaluated the effects of anesthesia on epileptic activity, classifying three types of anesthesia: proconvulsant anesthesia (nitrous oxide, methohexital, morphine, meperidine, fentanyl, sufentanil), anticonvulsant anesthesia (thiopental, midazolam, lorazepam), and others that are both pro- and anticonvulsant (halothane, enflurane, isoflurane, etomidate, diazepam, ketamine, propofol, local anesthetics). These authors concluded that the patient population (epileptic or non-epileptic), the method of documentation (EEG study or clinical observation), and the method of EEG analysis (cortical or depth electrodes) must be considered properly to analyze the proconvulsant and/or anticonvulsant properties of an anesthetic or analgesic drug. Moreover, biologic variability plays an important role in determining individual patient's responses to anesthetic and analgesic drugs, as well as variations in the responsiveness of inhibitory and excitatory neurons to the central depressant effects of these drugs.

The effect of anesthesia on MEG findings has been scarcely investigated. Methohexital-induced epileptiform discharges detected by MEG in patients with medically intractable epilepsy have been reported (Kirchberger et al., 1998), but this drug was not given to our patients. The potential impact of anesthesia in our study population is difficult to ascertain because the study population is small, none of the patients had clinical history of seizures, most MEG studies were performed under anesthesia, although none of the children was premedicated, and three different anesthetic regimens were used. However, the combination of midazolam 0.3 mg/k and propofol 1 mg/kg (type C protocol) was the anesthetic regimen that apparently resulted in a lower interference with epileptiform activity. This observation is consistent with data of the study of Szmuk et al. (2003). In a retrospective review of 48 pediatric patients with intractable seizures undergoing MEG under anesthesia, chloral hydrate premedication and propofol maintenance resulted in a lower incidence of MEG failure.

According to the results from our study population, we observed that the perisylvian area shows higher epileptiform activity than the extraperisylvian area in the ASD group and in children with severe autism. In agreement with data of Lewine et al. (1999), MEG activities in both intraperisylvian and extraperisylvian areas for patients with PDD-NOS and patients with ASD were similar. The present study shows that MEG data may be useful for the differentiation of ASD and PDD-NOS, and Asperger's syndrome from autistic disorder. However, MEG activity was not useful to distinguish between low-moderate and severe ASD.

Our ASD patients show more epileptiform and epileptic activity than the normal population and this activity can be measured using MEG, which contributes to

the clinical classification of ASDs, which is consistent with neuroanatomic findings. Casanova et al. (2002) found significant differences between brains of autistic patients and controls in the number of minicolumns, in the horizontal spacing that separates cell columns, and in their internal structure. Specifically, cell columns in brains of autistic patients were more numerous, smaller, and less compact in their cellular configuration with reduced neuropil space in the periphery. Another study regarding cerebral chemistry found significant alterations in the NAA (*N*-acetyl-aspartate) in some regions that form the perisylvian area (cingulated gyrus, superior temporal gyrus) as well as the thalamus (Friedman et al., 2003). The lack of NAA would be indicative of the neuronal decline and viability. Similar data regarding the thalamus were found by our group (Perich-Alsina et al., 2002).

The detailed pattern of activity may be related to detailed symptoms as evidenced by different patterns in autism, Landau–Kleffner syndrome, and Rett's syndrome. In the hypothesis established by Morrell et al. (1995), epileptiform activity in Landau–Kleffner syndrome breaks the established cognitive function, similar to the regressive syndromes or cryptogenic forms which are characterized by their high epileptiform activity. Similarly in the primary forms, epileptiform activity would provoke a stop in the cognitive developmental process through synaptic pruning at neuronal connections, not acquiring language and communication, empathy and establishing the stereotypes which characterize AD. If the epileptiform activity in the mentioned areas is really a part of the pathogenesis of ASDs, then early diagnosis becomes imperative when faced with the suspicion of a possible ASD, because the use of anticonvulsant drugs during the first year of life in primary autism or early treatment during the beginning stages of the loss of acquisition in the cryptogenic forms would avoid such pathologies or would diminish the severity of the disorder.

It has been extensively recognized that autism often remains unrecognized and undiagnosed. In the interesting study of Filipek et al. (2000), a diagnostic algorithm based on DSM-IV and ICD-10 criteria is proposed. In accordance with these authors, we have also used DSM-IV, ICD-10 and CARS as reference criteria together with other age-dependent psychological tests. The present study shows that MEG epileptiform activity is frequently documented in children with early-onset ASD. The significance of this finding is that subclinical epileptiform activity is present especially in the perisylvian regions for many patients with ASD.

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