
Auditory Sensory Processing in Autism: A Magnetoencephalographic Study

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Background: *Patients with autism show clinical features suggestive of abnormal processing of auditory and other sensory information. We hypothesized that low-functioning autistic subjects present abnormalities in discriminating simple auditory stimuli at sensory system preconscious stages of cortical processing.*

Methods: *To verify our hypothesis, we used magnetoencephalographic measurements of mismatch field (MMF), which reflects the detection of a change in the physical characteristics of a repetitive sound. Fourteen patients (aged 8–32 years) who met DSM-IV diagnostic criteria for autistic disorder participated in an auditory oddball experiment. Ten healthy participants matched for age and gender acted as control subjects.*

Results: *Significant differences in cerebral responses between patients and control subjects were recorded. Whereas control subjects showed a clearly identifiable MMF, with distinct generators in the M100 brain wave with regard to latency, position, and strength, no identifiable MMF was present in the autistic group.*

Conclusions: *Our findings suggest that low-functioning autistic subjects present a dysfunction at preconscious stages of cortical auditory discrimination, playing a role in the abnormal processing of auditory sensory afferences. The attention independence of the MMF allows for exclusion of an effect related to impaired attention or task-related responses. Biol Psychiatry 2003;54:647–654 © 2003 Society of Biological Psychiatry*

Key Words: Autism, cortical discrimination ability, magnetoencephalography, mismatch field, automatic neural mismatch, sensory impairment

Introduction

Autism is a neuropsychiatric syndrome with an early onset. Clinical patterns seen in patients with autism fall within a continuum of severity, and it has been suggested that a dimensional concept of the autistic spectrum underlies the clinical, genetic, and pathophysiologic heterogeneity of the disorder (Wing 1987). Autistic behavior is seen in an increasing number of genetic and metabolic conditions (Bauman and Kemper 1994; Chugani et al 1999; Junaid and Pullarkat 2001; Nelson et al 2001; Stokstad 2001). A single underlying neuroanatomic substrate has not been conclusively defined, and various areas of the brain have been suggested as playing a role in the development of the typical clinical signs of autism (Kates et al 1998; Schaefer et al 1996; Stokstad 2001). Structural brain abnormalities have been identified in the cerebellum (Schaefer et al 1996), limbic structures (Bauman and Kemper 1994), brain stem (Rodier 2000), and temporal lobe gray matter (Rojas et al 2002). Despite the extreme diversity of underlying etiologies, converging evidence from structural brain imaging techniques points to a neurodevelopmental origin of the anatomic lesions seen in some autistic patients, suggested by a disruption of cortical proliferation, migration, and organization (Gaffney and Tsai, 1987; Piven et al 1990). Neuropathologic studies have revealed enlarged neurons in the septum, in deep cerebellar nuclei, and in the inferior olive. In some cases, anatomic changes can be so subtle that their recognition depends on evidence from functional imaging studies (Schifter et al 1994). Positron emission tomography (PET) studies have reported abnormal glucose metabolism in the temporal, frontal, or parietal associative cortices (Haznedar et al 1997; Horwitz et al 1988), as well as abnormal brain serotonin synthesis (Asano et al 2001; Chugani et al 1999). These findings seem to suggest that the difficulty in integrating input from a variety of sensory modalities seen in many patients with autism may be related to a dysfunction in associative cortices and subcortical structures. This hypothesis is corroborated by evoked potential studies reporting significant decrease in

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amplitude of cognitive brain responses related to information processing (Lincoln et al 1993).

Currently agreed-upon diagnostic criteria include qualitative impairment in social interaction, language, and communication skills, along with stereotyped patterns of behavior and a restricted range of activities (American Psychiatric Association 1994). Other symptoms almost universally reported are not considered necessary or sufficient for a diagnosis of autism. One of the most characteristic of these is an abnormal reactivity to a variety of sensory stimuli (Gillberg and Coleman 2000). Abnormal sensitivity to heat, cold, pain, or tactile stimuli is frequently reported. Abnormal behaviors related to hearing are part of most currently adopted diagnostic instruments (Lord et al 1997; Schopler et al 1980). Abnormalities appear in response to ordinary environmental noise or voice in general, possibly reflecting sensory modulation problems (Harris 1995; Ho et al 1999). These clinical features have stimulated the search for functional abnormalities along the auditory pathways (Lincoln et al 1995; Novick et al 1980).

The purpose of our study was to investigate the initial stages of auditory sensory processing through magnetoencephalographic (MEG) recordings of the mismatch field (MMF; Sams et al 1991) in autistic patients' functioning at the lower end of the symptomatic spectrum. The MMF and its electrical counterpart mismatch negativity (MMN) are a preperceptual physiologic measure of the central sound representation of the human brain (Näätänen and Alho 1997). The working hypothesis is that low-functioning autistic subjects present an abnormality in discriminating simple sound stimuli in early attention- and cognition-independent cerebral processes along the central auditory pathway.

Methods and Materials

Fourteen patients aged 8–32 years (mean 16 ± 9 years; 11 male and 3 female subjects) who met DSM-IV criteria for autistic disorder participated the study. There was no historical report of language regression. None of the patients demonstrated syndromic features on clinical examination. Handedness could not be reliably determined, although all appeared to be primarily right handed. Their level of functioning was measured with the Adaptive Behavior Inventory (Brown and Leigh 1986), a standardized instrument for the assessment of adaptive behavior composed of 150 items and including subscales of self-care, communication, social skills, and academic and occupational skills. The Adaptive Behavior Inventory yields an adaptive behavior quotient (ABQ) ranging from 38 (less than the .1 percentile) to 161 (greater than the .99 percentile) and a cut-off for probable mental retardation of less than 110 when normed against healthy controls or less than 69 if measured against a control population of subjects with known mental retardation.

The severity of autism was measured with the CARS (Childhood Autism Rating Scale; Schopler et al 1980), which is a 15-item scale that rates the severity of a variety of behaviors observed in autistic subjects, including hearing and verbal behaviors, and provides a score of 15–60 with cut-off of 33.

Two of the patients had epilepsy, which developed years after the onset of autistic symptoms; one patient was receiving valproic acid as an anticonvulsant at the time of the study. On neuroimaging, one patient had bilateral ventricular dilation and one a Chiari I malformation.

A group of 10 matched healthy control subjects (aged 7–35 years, mean 19 ± 11 years, 8 male and 2 female subjects) were also studied. All patients and control subjects had normal hearing and normal brainstem auditory evoked responses, demonstrating good auditory propagation along subcortical auditory pathways and relays (Rossini et al 1980; Sohmer and Student 1978).

The S. Giovanni Calibita-Fatebenefratelli Hospital Ethics Committee approved the experimental paradigm, and all subjects or their parents gave informed consent.

MEG Procedure

All subjects were allowed a period of adaptation to the testing environment to maximize cooperation and minimize psychologic discomfort to the novel and unusual situation. A parent was always allowed inside the recording room.

Each subject participated in an acoustic oddball paradigm, in which infrequent deviants were randomly interspersed with a probability of .08 among monotonously repeated standard stimuli (interstimulus interval 731 msec). Standard stimuli were tone bursts of 1000 Hz frequency and 100 msec duration, 50 dB above subjective threshold for control subjects and set at a sound pressure level of 90 dB for patients. Deviants differed from standards tones in their frequency (1200 Hz). Data were acquired in four blocks each lasting 4 min. Subjects were lying on a bed in a magnetically shielded room (Vacuum Schmelze GmbH, Hanau, Germany) with the head fixed by a vacuum cushion. Sounds were generated by a personal computer and presented to the left ear via a plastic tube. The MEG recordings were performed with a 28-channel system, covering an area of about 180 cm² as described in a previous study (Tecchio et al 2000). A single sensor position was used to record the auditory evoked fields (AEFs), centered over the midtemporal lobe contralateral to the stimulated ear, according to previously published data (Pantev et al 1995; Tecchio et al 2000). In all the control subjects, such a position was able to map out the two extrema of both the brain waves under examination (M100, MMF), given the proximity of the position of the respective cerebral generators (Mathiak et al 2002; Sams et al 1991). Sensor position with respect to the subject head was detected by using five firmly taped current-supplied coils, with digitized three-dimensional positions (Polhemus Isotrak, Colchester, Vermont) at the end of the recording session. Monaural stimulation and contralateral recording were chosen to minimize the recording time, according to the lack of specific lateralization and interhemispheric asymmetries reported in previous studies in control and autistic subjects (Kemner et al 1995); this allowed for a reasonable level

Table 1. Clinical Data

Subject	Sex	Age	Diagnosis	CARS	ABQ (%)
S1	M	9	Autism, lateral ventricle dilatation	53	53 (<.1)
S2	M	11	Autism	43	52 (<.1)
S3	M	29	Autism	40	44 (<.1)
S4	M	19	Autism, epilepsy	45	41 (<.1)
S5	M	8	Autism	40	64 (.8)
S6	F	32	Autism	33	47 (<.1)
S7	M	25	Autism	43.5	40 (<.1)
S8	F	18	Autism, epilepsy	40	43 (<.1)
S9	M	13	Autism	42.5	55 (.1)
S10	M	14	Autism, epilepsy	45.5	52 (<.1)
S11	M	9	Autism	47.5	56 (.2)
S12	M	8	Autism, Chiari Type I malformation	46	62 (.2)
S13	F	23	Autism	32	47 (<.1)
S14	F	12	Autism	44	51 (<.1)

Patients profile in terms of sex, age, diagnosis, Childhood Autism Rating Scale (CARS), and Adaptive Behavior Quotient (ABQ) scores. For the ABQ, corresponding percentile value within the normal population is indicated in brackets.

of collaboration in all control subjects and in most of the autistic patients.

MEG Data Analysis

Continuous acquisition in response to auditory stimuli (250-Hz sampling rate, .48- to 64-Hz bandwidth) was performed. Approximately 1200 artifact-free trials were acquired, digitally filtered from 1–40 Hz and averaged separately for standards and deviants. The amplitude of the AEFs was calculated for each channel with respect to a baseline level chosen as the mean value of the 50-msec prestimulus epoch. The power summed over all channels has been considered for individual component identification. The M100 component was defined as the first power maximum following the 50-msec latency, evaluating the corresponding field distribution polarity (Pantev et al 1995). For MMF identification, the channel-by-channel difference between deviant and standard responses was computed. The MMF was identified as the first power peak of the difference traces at latency following the M100.

When brain responses tracked in a millisecond-by-millisecond mapping detected a dipolar magnetic field distribution, cortical generators subtending M100 and MMF components were localized using a single equivalent current dipole (ECD) model inside a homogeneously conducting sphere (Natanen and Alho 1995). The field distribution evaluated in a time epoch spanning from 8 msec before to 8 msec after the peak of the M100 and of the MMF, was used to calculate the ECD position, strength, and direction using a fixed dipole model. The single dipole is considered a standard model for these two component generators, suitably representing the subtending activation (Imada et al 1993). Localization results were accepted only if the explained variance was above 90%. The ECD position was expressed in the individual cartesian coordinate system, defined as follows: x axis passing through right and left preauricular points (A2 and A1, respectively), outgoing rightward; the positive y axis through the nasion; and the z axis perpendicular to the point of bisection between the x and y axes. For comparison of source position in

the subjects, the three coordinates were normalized to a standard head ($x(A1 / A2) = 68$, $y(\text{nasion}) = 90$, $z(\text{vertex}) = 114$ mm); this kind of rescaling was suitable for the limited cerebral region involved.

Statistical analysis for differences between M100 and MMF was performed in controls by comparing latency, strength, position, and direction of the cerebral generators by Student's *t* test. The same procedure was used for comparing M100 source in controls and autistic subjects. The comparison of the MMF in control and autistic subjects was performed by Student's *t* test on the integral of the total power measured on the deviant minus standard signal in the 150-msec time window starting with the M100 latency, divided by the variance in the 100-msec pretrigger interval (MMF total power).

The relationship between cerebral source characteristics and age has been evaluated for control and autistic subjects separately using linear correlation coefficients.

Results

Patients' Clinical Profile

None of the patients had normal language skills, and all lived at home with their parents. The measured ABQ placed all autistic patients in the mentally retarded range, when compared with both healthy and the mentally retarded normative population for this specific scale (Table 1). All but two patients scored in the severely affected range on the CARS (Table 1). Verbal communication skills were moderately to severely impaired in all patients, as assessed by the verbal communication subscale of the CARS, and manifested as nonfunctional echolalia or simple utterances or vocalizations. Likewise, all patients demonstrated abnormalities in their hearing response, as assessed by the hearing response subscale of the CARS with abnormal responses to sound or noise.

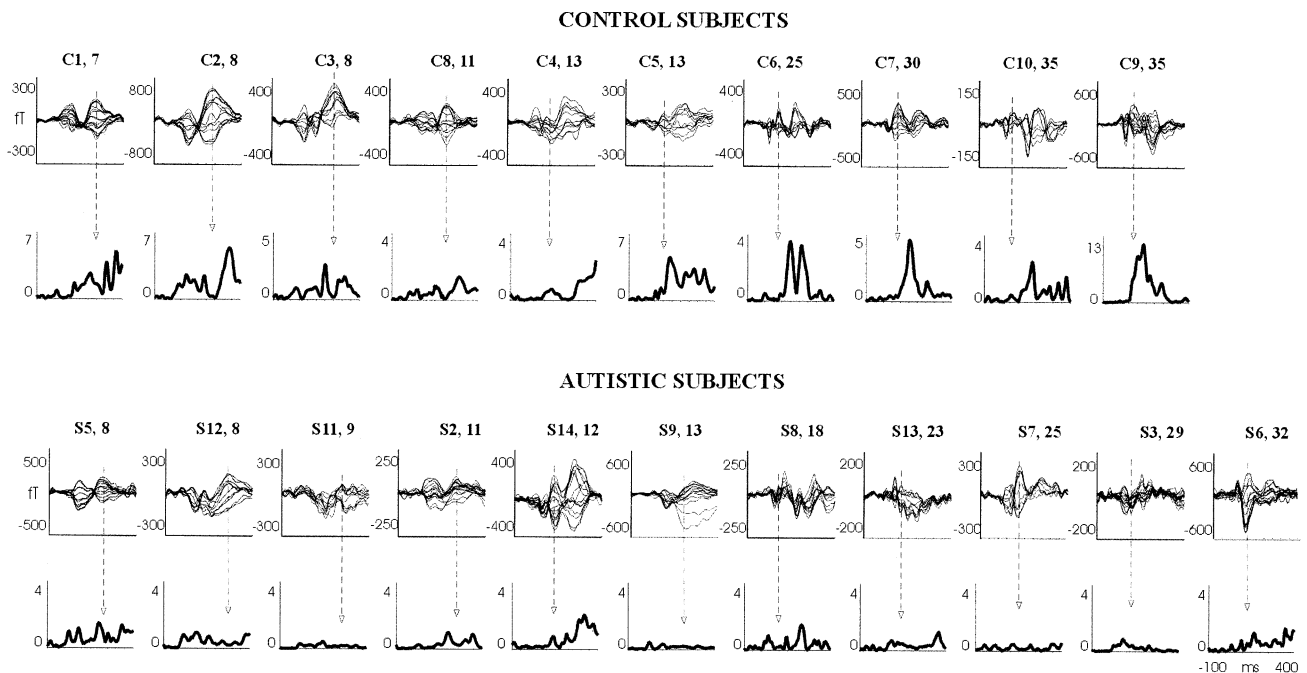


Figure 1. In control and autistic subjects, auditory responses to standard stimuli are superimposed as recorded by each channel in the 500-msec time window, with 100-msec prestimulus (first and third rows). Age for each subject is indicated. Magnetic field scale in fempto-Tesla are indicated for each subject. The vertical line indicates M100 component latency. In the second and fourth rows for each subject, the mismatch field total power is shown (pure number). Note the presence of clear maximum successive to M100 latency in all control subjects.

Neurophysiologic Assessment

Of the 14 autistic subjects, 3 (subjects S1, S4, and S10) were unable to tolerate testing conditions. The remaining patients, following an initial adaptation to the environment, were able to cooperate fully without sedation for the duration of each recording block (4 min each).

Evoked field waveforms are shown in Figure 1. No differences between control and autistic subjects were found for M100 latencies or strength, suggesting that

cortical sensory processing in the primary auditory cortex is unaffected (Table 2); however, the localization of the sources of the M100 revealed a significantly deeper position for autistic patients with respect to control subjects ($p = .001$, Table 2). Moreover, the M100 position resulted significantly more superficial with increasing age in control subjects ($R^2 = .35$, $p = .05$), and it was not dependent on age in autistic subjects ($R^2 = .04$, $p > .2$). Latencies of the M100 component showed a significant

Table 2. Cerebral Sources Characteristics

	Lat (msec)	x (mm)	y (mm)	z (mm)	Str (nA.m)	P _x (nA.m)	P _y (nA.m)	P _z (nA.m)
Control Subjects								
M100	129	37	13	67	11	.21	-.59	-.73
MMF	210	28	21	67	24	.31	-.60	-.60
Difference	81 ^b	-9	8 ^a	0	13 ^a	.10	.01	.13
<i>p</i>	<.01	.09	.03	>.2	.01	.085	>.2	.050
Autistic Subjects								
M100	114	22 ^b	7 ^a	61	17	.30	-.75	-.28 ^b
<i>p</i>	>.2	<.01	.016	.14	.16	>.2	.16	<.01

Average latency (Lat), location (x, y, z), strength (Str), and direction (expressed by the three components of the strength unitary vector, p_x, p_y, p_z) of dipolar sources in autistic patients and control subjects. In autistic patients, as no MMF was identified, only M100 data are presented. In control subjects, average difference between cerebral sources of MMF and M100 on the three axes is computed to simplify their comparison (MMF - M100, Δx < 0 is MMF deeper source, Δy > 0 more anterior, Δz > 0 higher).

MMF, mismatch field.

^a*p* < .05

^b*p* < .01

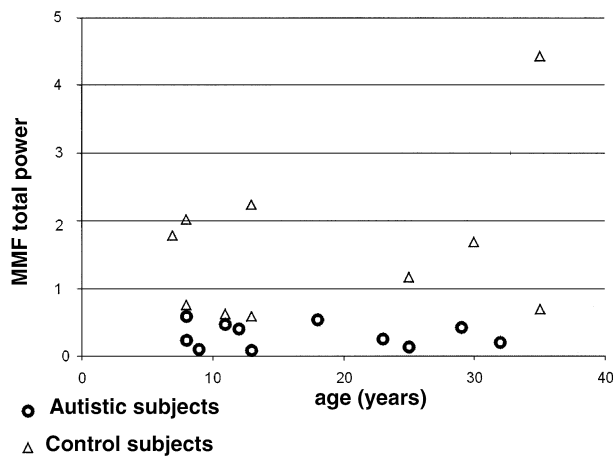


Figure 2. Mismatch field (MMF) total power in control (triangles) and autistic subjects (circles), scattered in relation to individual age.

decrease as a function of age both in control and autistic subjects. In fact, Pearson correlation analysis showed a significant M100 latency decrease for subjects younger than 18 (13 subjects, age interval 7–18 years, mean 10.3 ± 3.1 years, $r = -.53$, two-tailed $p = .049$) and no significant dependence for subjects older than 18 (8 subjects, age interval 25–38 years, mean 30.0 ± 4.8 years, two-tailed $p > .2$). Considering together autistic and control subjects, mean latencies were 156 ± 41 msec in subjects aged less than 18 years and 91 ± 13 msec in subjects older than 18 years.

The MMF total power was significantly lower in the autistic subjects with respect to control subjects ($p = .008$, Figure 2). MMF peak was clearly identifiable in all control subjects (Table 2, Figure 1), and cerebral sources of the

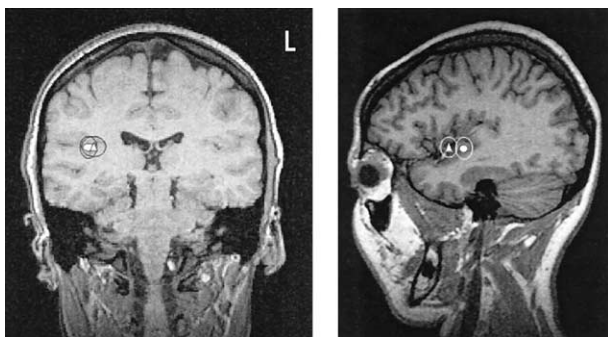


Figure 3. Position of the equivalent current dipole related to the generators of M100 (circle) and mismatched field (triangle) components are shown for a representative control subject. The SD of the normalized coordinates of the other control subjects for the two components are also shown. The ellipse's axis represents the SD of x and z coordinates in the axial view, and the DS of y and z coordinates in the sagittal view.

MMF were stronger than the ones activated by standard stimuli (Table 2), in agreement with previous results (Levanen et al 1993; Sams et al 1991). The cerebral sources of the MMF in the control group were consistently more anterior (approximately 1 cm) to those activated by standard stimuli (Table 2, Figure 3) as reported in previous studies (Csèpe et al 1997). In addition, localization of the generator subtending the MMF agreed with an activation of the superior temporal gyrus. For the ECD direction, the sources activated by deviant tones pointed more laterally than those activated by standards (Table 2).

Discussion

In this series, all of the autistic subjects showed a normal latency response and activated source strength to repeated standard stimuli, indicating normal signs of cortical auditory function at the level of the superior temporal gyrus. The independence of M100 position and age in autistic patients, compared with control subjects, and its localization in deeper temporal regions in younger control subjects, may be explained by an impaired maturation of the tonotopic organization of the auditory cortex in autistic subjects. Concurrently, the preserved dependence of M100 latency on age (Albrecht et al 2000; Gomes et al 2001; Rojas et al 1998) in the autistic subjects and the similar M100 source strength in the two groups indicate that the possible loss in maturation of the tonotopic organization is not associated with altered arrival of the auditory signal to the cortex. This finding needs confirmation with a larger data set and on normative longitudinal data on the tonotopic representation during development.

Unlike control subjects, autistic patients demonstrated a significant reduction in amplitude or the absence of the MMF. This component is known to depend on the memory trace formed by the preceding auditory stimulus, and represents a neurophysiologic measure of auditory sensory memory. Its stability across a wide age range makes it suitable for the comparison of patients with different developmental levels (Cheour et al 2000). Although a substantial portion of the MMF response is generated within the auditory cortex (Alho 1995), studies have identified a frontal component (Giard et al 1990), suggesting that the change detection signal could trigger frontal mechanisms of attention switch (Näätänen 1990).

The normal latency and amplitude of the M100 suggest that autistic subjects have no impairment in primary auditory cortical responsiveness. This evidence, combined with the recent report of a normal P50 auditory gating in high-functioning autistic subjects, suggest that, at least in some subsets of patients, the unusual reaction to stimuli may not be related to altered filtering of sensory input (Kemner et al 2002). Studies of the early components of

the event related potentials (N1 and P2), known to be dependent on stimulus characteristics (Adler and Adler 1991) and nonsensitive to task directed attention, have demonstrated results similar to ours in absolute amplitude and latencies for a group of autistic subjects functioning in the lower range of ability. Data from our study confirm previous findings in children with tuberous sclerosis complex, autism, and temporal lobe lesions in whom abnormal MMN is reported (Seri et al 1999). In the same study, no MMN abnormalities were found if lesions were elsewhere in the cerebral cortex. This might result from an interference of the anatomic lesions in the temporal lobes on auditory sensory processing. The abnormal MMF in autistic patients is indicative of a disruption in the ability to discriminate the physical properties of two consecutively presented stimuli. This has also been described in patients with schizophrenia (Kreitschmann-Andermahra et al 1999) and in patients with developmental language disorder and mental retardation (Holopainen et al 1998). Of note is that in the latter two populations, abnormalities in MMN were related to impaired language skills regardless of the children's cognitive status.

One previous article reported no abnormalities in the MMN of 20 autistic children with near normal IQ (Kemper et al 1995). The apparent discordance with our results is probably due to a variety of factors, including the stimulus characteristics, the recording methods, and, more important, to the higher functioning of the subjects recruited in the study.

Previous studies using cognitive ERPs in autistic subjects focused on later stages of information processing and reported a significant decrease in amplitude of the P3b component, suggesting an abnormality in the cognitive elaboration of auditory stimuli (Lincoln et al 1993). The interpretation of this finding, and those of other studies involving behavioral responses in autistic patients, has the inherent difficulty of the variability in the response (Courchesne et al 1985; Picton 1992) in a population in which full cooperation and attention steadiness are difficult to obtain and control for. In this respect, the attention-independence of the MMF (Naatanen et al 1993) allowed us to exclude the possibility that the changes we have documented may be related to abnormal attentional processing (Ciesielki et al 1995). In addition the P3, a cognitive task-dependent response reflecting the activity of distributed brain networks, provides us with information on later stages of information processing.

Based on our findings, we can hypothesize a pathogenetic role of abnormal auditory discrimination in the development of some of the autistic symptomatology. This might not be exclusive to the auditory modality. In autistic children, impaired auditory discrimination ability in pre-conscious cortical processing stages may hinder the devel-

opment of more complex connections. In particular, it could affect functional development of physiologic tonotopic organization at auditory cortical level. Alternatively, reduced auditory discrimination could be secondary to more complex developmental abnormalities. A disruption of brain areas such the amygdala and the hippocampus (Kates et al 1998; Sparks et al 2002; Stokstad 2001) in early stages of development could alter memory and emotion-guided motivational behavior, accounting for the altered processing of environmental stimuli and constituting a basis for the inability to develop correct sensory discrimination.

We believe we have provided further evidence supporting an abnormal auditory processing in a subset of autistic children, although we are aware that a generalization of our results to the entire "autistic spectrum" may not apply to the clinical reality of higher functioning patients, for whom higher order processes are mainly involved and appropriately tested. Our findings need to be replicated in a larger patient sample and along the entire autistic spectrum. Given the presence of "autistic" features in other nosographic entities (Asano et al 2001; Gillberg 1998; Rojas et al 2001; Seri et al 1999), the inclusion of other patient groups in future studies would be essential. In particular, protocols involving other types of mental retardation syndromes with cognitive levels similar to our group of autistic subjects are needed to further determine the specificity of our findings.

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