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Peripheral auditory asymmetry in infantile autism

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Abstract

Difficulty in filtering relevant auditory information in background noise is one of the features of autism. Auditory filtering processes can be investigated at the peripheral level as they are hypothesized to involve active cochlear mechanisms which are regulated by the efferent activity of the medial olivocochlear (MOC) system. The aim of the present work was therefore to assess these peripheral auditory processes in 22 children and adolescents with autism compared with age- and gender-matched normal controls. Active cochlear mechanisms were evaluated with transiently evoked otoacoustic emissions (TEOAEs) and MOC system efficiency was assessed via TEOAEs which are decreased when stimulating the contralateral ear with noise. The MOC system evaluation was performed on 18 of the 22 children. In both studies, results were analysed according to age (from 4 to 10 years and from 11 to 20 years). The main result concerns the asymmetry of the efferent system which differs in individuals with autism. Several neural processes might be hypothesized as involved in the results obtained as the MOC system which originates in the brainstem received regulating controls from upper brain structures including auditory cortex. Lateralization abnormalities at the auditory periphery may reflect indirectly a problem at a higher level of auditory processing. A second important result shows a decrease in TEOAE amplitude with age, in patients, that may correspond to a decrease in hearing sensitivity.

Introduction

Autism is a behaviourally defined syndrome characterized by impairment of social interaction, deficiency or abnormality of speech development and limited activities and interests (American Psychiatric Association, 1994). The prevalence rate is about 4.5–5/10 000 (Fombonne & Mazaubrun, 1992). As infantile autism involves developmental abnormalities of motor, sensory and cognitive functions, a correspondingly large number of different neuroanatomical systems have been demonstrated to be maldeveloped (see review in Gillberg & Coleman, 2000).

Atypical reactions to the sensory environment are often reported in children with autistic behaviour. While all modalities are affected, these abnormalities are particularly evident in hearing (Goldfarb, 1963; Ornitz, 1974; Dahlgren & Gillberg, 1989). These symptoms include not only hyporeactivity to auditory stimulation but also hyperacusia (Coleman & Gillberg, 1985; Rosenhall *et al*., 1999) and difficulty filtering out background noise involved in targeting the pertinent auditory signal in the environment (Grandin & Scariano, 1989). These processes are essential for appropriate use of language in a social context.

The ability to improve the signal-to-noise ratio and thus to filter-relevant auditory information involves regulation of cochlear activity by the central nervous system via descending auditory pathways (Feliciano *et al*., 1993). The active micromechanical properties of the outer hair cells of the organ of Corti underlie the sensitivity of auditory receptors and hence modulate afferent volley firing from the inner hair cells. The outer cells are synapsed directly by efferent neurons originating in the vicinity of the nuclei of the superior olivary complex corresponding to the medial olivocochlear (MOC) bundle (Warr & Guinan, 1979; Eybalin, 1993). The activity of the MOC bundle itself is regulated by information descending from the upper part of the brain.

The contractile activity of the outer hair cells can be evaluated in humans. Triggered by transient auditory stimulations, it generates acoustic signals which can be recorded in the external ear canal (Kemp, 1978). The transiently evoked otoacoustic emissions (TEOAEs) thus obtained in one ear can be reduced by stimulating the contralateral ear with white noise. It has been demonstrated that this contralateral suppression effect is mediated via the MOC system (Collet *et al*., 1990a, b; Veuillet *et al*., 1991). Such a method makes possible therefore the evaluation of the MOC system activity under noninvasive conditions.

Using this type of test, it has been shown that the MOC system improves signal-to-noise ratio (Micheyl *et al*., 1995) and speech-in-noise intelligibility (Giraud *et al*., 1997). In view of the auditory disturbances presented by individuals with autism, the hypothesis of possible dysfunction of the MOC system has been proposed (Collet *et al*., 1993) based on preliminary findings of 11 autistic adults who demonstrated a decrease in MOC system activity.

The aim of the present study was to assess TEOAEs and their modification by the MOC system in children and adolescents with autism compared with age- and gender-matched normal controls. As

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auditory sensitivity is known to increase gradually during childhood until about 7–10 years of age (Spreen *et al*., 1995), two age groups (4–10 years and 11–18 years) were studied to take into account any possible developmental influence.

Materials and methods

Subjects

This study was carried out with the agreement of the Ethics Committee of the Léon Bérard Center of Lyon, obtained on 20 January 1998. Written consent was required from parents and children (when they were able to give their opinion) before testing. The tests used were noninvasive and painless, and could be stopped whenever requested by parents or children.

Results were obtained in optimal conditions for 22 of the 31 autistic children and adolescents tested (aged from 4 to 18 years; mean age (SD) = 10.57 (4.7) years). All were diagnosed according to DSM IV criteria (American Psychiatric Association, 1994). They displayed mild to moderate mental retardation (mean IQ (SD) = 63 (23)). All were able to sit quietly during our objective auditory measurements. As the study focused on laterality, only right-handers were included. Their handedness laterality quotients (LQs) assessed using the Edinburgh Handedness Inventory (Oldfield, 1971) were all positive, indicating right-hand preference.

None of the patients had known auditory, neurological or associated disorders or was receiving medication. Tests were carried out at three different hospitals, but always in a quiet room with the same portable apparatus.

Two studies were performed in succession. In the first, active cochlear mechanisms were evaluated by measuring TEOAEs. In the second study, the efferent activity of the MOC system was assessed by measuring the contralateral suppression effect, i.e. the reduction in TEOAE amplitude in one ear upon stimulation of the opposite ear. This second study took longer to record. Four of the 22 patients who participated in the first study were not able to comply with the requirements of prolonged session and results were therefore obtained for 18 patients.

For both studies, children with autism were matched for age (± 1 year) and gender with right-handed control children (mean LQ (SD) = 83 (23) for the control group involved in the first study and LQ (SD) = 84 (23) for the control group involved in the second study).

In both studies, data analysis was performed first on the whole group and then according to age by separating each group into two subgroups aged 4–10 years and 11–18 years, respectively (see Table 1 for details).

Otoacoustic emission recording

TEOAEs were recorded using the ILO88 Otodynamics software system (www.otodynamics.com). This system, described in detail by Kemp *et al*. (1990), allows measurement of ear-canal sound pressure variations following transient acoustic stimulation. The probe used comprised a Knowles 1843 microphone and a BP1712 transmitter embedded in a plastic ear plug. The probe was inserted into the subject's ear canal using a foam eartip. Acoustic stimulation was delivered in the form of 80 μs unfiltered clicks at 80 dB sound pressure level (SPL) for TEOAE measurements and 63 dB SPL for MOC system evaluation, presented at a rate of 50/sec. TEOAE amplitudes were recorded in both ears (in random order) at 63 dB SPL with a response window set at 3.0–20 ms, using the linear method as defined by the ILO88 system. To avoid artefacts due to greater stimulus intensity, a nonlinear method (Kemp *et al*., 1990) was employed at 80 dB SPL and the response window was set at 2.5–20 ms. Each TEOAE resulted from an average of 250 acoustic responses.

MOC system evaluation (TEOAE contralateral suppression)

TEOAE recordings were repeated three times in the presence and absence of a contralateral broad-band noise stimulus of 35 dB SL (sensation level) generated through another probe by the ILO88 system. The contralateral effect elicited from the MOC bundle activation corresponds to the average of these three measurements. Suppression was determined by subtracting TEOAE amplitude without contralateral stimulation from TEOAE amplitude with contralateral stimulation. This difference in amplitude is expressed as a negative value in dB. The lower this value, the greater the MOC system efficiency.

Data analysis

Each set of variables (TEOAE amplitude, TEOAE contralateral suppression effect) was analysed using a repeated-measures multivariate analysis of variance (MANOVA), with group (control vs. autism) and age (before vs. after 10 years) as the between-subjects variable, and ear (right vs. left) as the within-subjects variable. Significant effects were followed by *post hoc* comparisons using Tukey's HSD test.

Pearson product moment correlation was also used to assess the relationship between TEOAE amplitude and contralateral suppression effect.

Results

TEOAE amplitude, asymmetry and age effect

Mean TEOAE amplitudes obtained in right and left ears of both autistic and control subjects, before and after 10 years of age are

TABLE 1. Characteristics of the two samples of children with autism involved in the studies

Study	Age span of group (years)	Subjects (*n*)	Sex ratio male/female	Age (years)	Laterality quotient	Intelligence quotient
I	4–18	22	16/6	10.6 ± 4.5	79.9 ± 33.5	62.8 ± 21
	4–10	11	9/2	6.7 ± 1.7	84.7 ± 14.6	71.7 ± 26.4
	11–18	11	7/4	14.5 ± 2.4	79.4 ± 43	54.6 ± 9.6
II	4–18	18	14/4	10.2 ± 4.8	83.2 ± 22	66.2 ± 22.7
	4–10	11	9/2	6.7 ± 1.8	84.7 ± 14.6	71.7 ± 26.4
	11–18	7	5/2	15.7 ± 1.5	81.43 ± 30	57 ± 11.5

Data are presented as means ± SD.

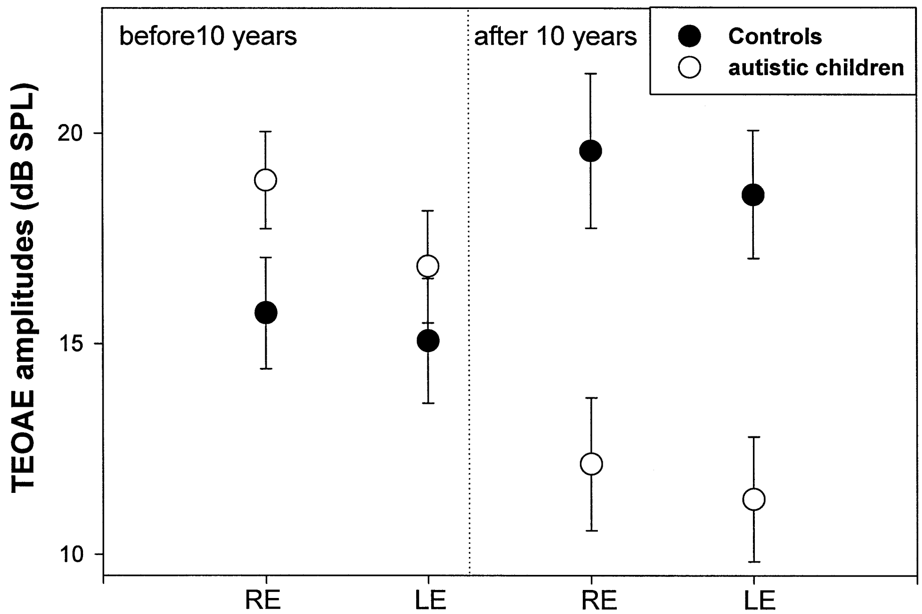

FIG. 1. Means and standard error bars of transiently evoked otoacoustic emission (TEOAE) amplitudes, in both ears (right ear, RE; left ear, LE) of autistic and control subjects, according to age (before and after 10 years).

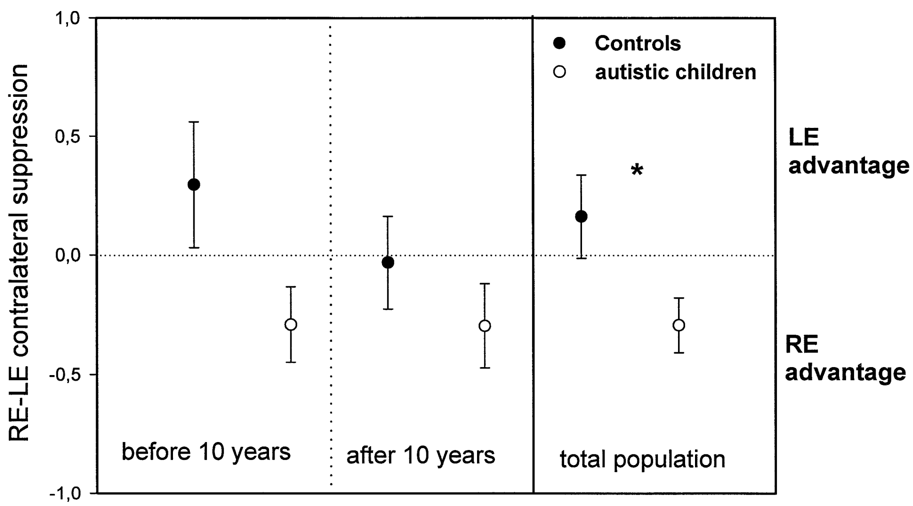

FIG. 2. Means and standard error bars of the interaural difference of transiently evoked otoacoustic emission (TEOAE) suppression effect, in autistic and control subjects according to age (before and after 10 years). The upper part of this figure represents a medial olivocochlear (MOC) system left ear (LE) advantage and the lower part, a MOC system right ear (RE) advantage.

represented in Fig. 1. The ANOVA results indicated a significant main effect of ear ($F_{1,40} = 5.7$; $P < 0.05$) due to greater TEOAE amplitudes in right than in left ears in both groups of subjects at all ages. There was also a significant group–age interaction ($F_{1,40} = 12.3$; $P < 0.002$), due to smaller TEOAE amplitude in patients than in controls after 10 years of age ($P < 0.003$; Tukey's *post hoc* test) whereas no significant intergroup difference was found before 10 years of age.

MOC system functioning, asymmetry and age effect

The overall ANOVA performed on the TEOAE contralateral suppression effect indicated mainly a significant group–ear interaction ($F_{1,32} = 4.94$; $P < 0.05$). Separate analysis of each group showed that children and adolescents with autism displayed a significantly greater suppression effect on the right ear than on the left ($F_{1,32} = 3.9$; $P < 0.05$) whereas no significant left–right difference was found in controls. Moreover, analysis performed on each ear separately did not show any significant between-subject difference.

Figure 2 shows the interaural difference in contralateral TEOAE suppression effect (suppression on the right ear minus suppression on the left ear). The overall ANOVA performed on this interaural index indicated a significant main effect of group ($F_{1,32} = 4.9$; $P < 0.05$) without effect of age. Autistic and control subjects had opposite patterns of asymmetry, with negative patterns of asymmetry for children with autism due to the significantly greater suppression effect on the right than on the left ear and positive patterns of asymmetry for control children due to a nonsignificant tendency for a greater suppression effect on the left ear than on the right.

TEOAE amplitude and MOC system functioning

Results concerning MOC system functioning appeared independent of TEOAE amplitudes, as no significant correlation was observed between TEOAE amplitude and contralateral TEOAE suppression in autistic subjects (RE: $r = -0.11$, ns; LE: $r = -0.03$, ns) or controls (RE: $r = 0.01$, ns; LE: $r = -0.07$, ns).

Discussion

TEOAE amplitudes

A clear asymmetry of TEOAE amplitudes was found in all subjects regardless of their age, with TEOAE amplitude greater for the right ear stimulation than for the left ear stimulation. This result in normal subjects is in agreement with our previous data obtained on 70 young right-handers demonstrating TEOAE amplitude to be right-predominant (Khalfa *et al*., 1997). This TEOAE asymmetry could reflect a lateralization of the active cochlear mechanisms as TEOAE corresponds to outer hair cells' contractile activity (Brownell, 1990). Outer hair cells could then be more efficient, reactive and/or numerous in the right than in the left ear. This functional cochlear asymmetry could also be related to a greater vulnerability of the left ear to auditory damage, as, in normal subjects, the left ear was the most susceptible to exhibit hearing loss (Glorig, 1958; Axelsson *et al*., 1981).

Different age-related evolutions of TEOAE amplitudes were found according to group. Controls did not show any significant modifications of amplitude with age. The only developmental data previously reported did not concern children. They indicated that TEOAE amplitude decreases during the first year of life (Engdahl *et al*., 1994) and that TEOAE are of greater amplitude in preterm neonates and children than in adults (Collet *et al*., 1990a, b; Norton & Widen, 1990; Smurzinski *et al*., 1993). Further studies are needed on large populations of normal children with narrow age grouping to clarify the influence of maturation on peripheral mechanisms. Unlike in controls, TEOAE amplitude decreased with age in children with autism. As a disruption of outer hair cell function (Patuzzi & Rajan, 1992) results in TEOAE amplitude decrease, the smaller TEOAE emissions' amplitudes in older autistic children may indicate an early decrease in hearing sensitivity with increasing age in autism.

TEOAE amplitude contralateral suppression

The results on MOC system lateralization demonstrate an abnormal pattern of peripheral auditory regulation in children with autistic disorders. This might reflect indirectly a problem at an upper stage of sound processing. It is hypothesized that the brainstem may be involved in such dysfunction, as in accordance with Skoff *et al*.'s (1980) finding that the most common brainstem auditory-evoked potentials' abnormality was a prolonged III–V transmission-time on the left side in a group of autistic children. This suggests a possible dysfunction in the brainstem that may affect not only afferent pathways, but also efferent pathways function.

It has been shown previously in normal subjects, that right-handed adults demonstrate a right-ear advantage of MOC system functioning (Khalfa & Collet, 1996) whereas this asymmetry does not exist in left-handed adults (Khalfa *et al*., 1998a). Given that this lack of peripheral auditory asymmetry in left-handers parallels their greater bihemispheric language representation, i.e. less cortical lateralization compared with right-handers (Hécaen & Sauguet, 1971), and given that this system receives nerve fibres coming from this lateralized auditory cortex (Feliciano *et al*., 1993), it has been hypothesized that the asymmetry pattern of MOC bundle activity may be linked with more central asymmetry.

Our present results raise questions about these links throughout development, as handedness and hemispheric asymmetry are established in childhood (Orton, 1934; Peters, 1995), whereas, according to our results of normal children who did not display asymmetry of the auditory efferent system, it seems it is not the case for the relationships between central and peripheral asymmetry.

However, even if peripheral and central auditory asymmetries do not develop strictly in parallel, the efferent system asymmetry pattern seems to be impaired in pathology, presenting abnormal hemispheric lateralization, such as a learning disability (Veuillet *et al*., 1999b). The abnormal MOC system lateralization in children with autism may then be related to their abnormal hemispheric lateralization reported previously.

Indeed, children with autism generally exhibit left-hemisphere deficits (Prior & Bradshaw, 1979; Dawson *et al*., 1982; Bruneau *et al*., 1999), such as impaired language and communication, and right-hemisphere competence for both verbal, spatial and musical functions. For example, they often excel in discriminating pitch (Frith, 1989) and the absolute pitch incidence is one out of 20 among autistic individuals whereas it is one out of 10 000 in the general population (Sacks, 1995). Children with autism also performed as well or better than controls on a music-tone imitation task (Appelbaum *et al*., 1979).

The unusual MOC system asymmetry pattern seen in autistic children may then reflect indirectly more central auditory processing alterations. The asymmetrical filtering of the auditory afferent message may also influence the development of the auditory system.

Concerning the meaning of the efferent system functioning measure, it has been shown previously that the MOC system stimulation improves the detection of multitone complex in noise (Micheyl *et al*., 1995). The contralateral suppression measurement is also considered as a valuable tool that could help in clinical assessment of the auditory function, especially for identification of retrocochlear pathologies (Veuillet *et al*., 1999a). In children with autism, our results are not in favour of a decrease in MOC bundle functioning, as proposed in a preliminary study by Collet *et al*. (1993), as no difference was found between autistic and control children. This discrepancy could be due to the great diversity of the clinical patterns, including the varying degree of mental retardation observed in autism (Rutter & Schopler, 1992), and to the age of the small sample studied (11 subjects from 6 to 30 years but mainly adults in Collet *et al*., 1993). This absence of significant difference does not preclude any auditory abnormality in autism contrary to the abnormal efferent system lateralization pattern.

TEOAE amplitude and MOC system functioning

In this study, the auditory periphery has been assessed at the level of the cochlea and at the MOC system level, using both for the TEOAE recording. Given that the MOC system is known to regulate the active mechanisms of the cochlea, the TEOAE amplitudes may be dependent upon the strength of this efferent system. However, even if the MOC system regulates outer hair cell electromotility, its suppressive effect is not correlated with the amplitude of the TEOAEs in either the presence or the absence of contralateral acoustic stimulation activating this efferent system. This is in accordance with previous findings (Khalfa *et al*., 1998b). As a consequence, it was not surprising to find different results concerning TEOAE and MOC system functioning in autism, such as the fact that MOC system asymmetry and evolution with age appeared to be different from results on TEOAE amplitudes.

Conclusion

A first important result of the present study concerns the asymmetry of low-level auditory processing which differs in children with autism. This unusual MOC system asymmetry pattern observed in autistic children may reflect indirectly more central auditory processing alterations involved in their atypical auditory reactivity.

A second important result shows a decrease in TEOAE amplitude with age which might correspond to a decrease in hearing sensitivity with increasing age.

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Abbreviations

ANOVA, analysis of variance; IQ, intelligence quotient; LQ, laterality quotient; MOC, medial olivocochlear; SPL, sound pressure level; TEOAE, transiently evoked otoacoustic emission.

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