Abnormal peripheral auditory asymmetry in schizophrenia

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Abstract

Objective—Auditory processing difficulties have been reported in schizophrenia. This study explores peripheral auditory function in patients with schizophrenia in whom certain early disturbances of auditory message filtering have been found and may be associated with certain abnormalities which are particularly localised in the left temporal lobe.

Methods—Otoacoustic emissions, including click evoked and spontaneous emissions and measurements of functioning of the medial olivocochlear efferent system were obtained from 12 chronic schizophrenic patients and compared with normative data recorded from 12 normal controls.

Results—Otoacoustic emission amplitudes and medial olivocochlear functioning were similar between the normal controls and schizophrenic patients; the schizophrenic patients did, however, differ from the normal controls in otoacoustic emission intensity and in medial olivocochlear asymmetry. A tendency to a higher number of spontaneous peaks, and a significantly higher click evoked otoacoustic emission response amplitude were found in the right ear compared with the left ear of schizophrenic patients. For the medial olivocochlear system, whereas normal controls showed greater attenuation in the right than in the left ear, schizophrenic patients lacked such an asymmetry.

Conclusion—In the absence of any attention task, the findings show disturbed peripheral lateralisation in schizophrenia of mechanisms involved in auditory information filtering. Such a lack of right ear advantage in medial olivocochlear functioning may thus be a peripheral reflection of central lateralisation anomalies.

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Keywords: schizophrenia; auditory processing; asymmetry; medial olivocochlear efferent system; otoacoustic emissions; lateralisation

Schizophrenia is a clinical syndrome highly characterised by cognitive dysfunctions. But severe auditory perception deficiencies consistent with hypersensitivity to external stimuli are also reported.¹ Deficient auditory processing has been widely reported in schizophrenia and such defects clearly appeared in auditory evoked responses. Schizophrenic patients show attenuation of the scalp recorded P300 re-

sponse,^{2,3} the greatest difference with normal controls occurring at left temporal electrode sites.^{4,5} Another electrophysiological abnormality is that the P50 component is less reduced in response to repeated stimulation, suggesting a deficit in the control of sensitivity to auditory stimuli.⁶⁻⁸ Abnormal mismatch negativity generation has also been reported in schizophrenic patients,⁹⁻¹¹ particularly in the left hemisphere.¹² This is consistent with a deficit in early cortical mechanisms of auditory sensory analysis. Finally, the auditory brainstem responses occurring within 10 ms of stimulation can also be affected in schizophrenia, with missing peaks or prolonged latencies.¹³ All in all, it seems that the early stages of auditory processing and perception are not intact in schizophrenic patients and that the underlying dysfunction may be an inability to properly filter the inflow of information from the environment.^{14,15} This could lead to a decrease in ability to focus on external sensory stimuli and to the hyperawareness of background noise described in schizophrenic patients.¹⁶ Although electrophysiological studies tend to point to a disruption of initial encoding due to defective inhibitory mechanisms, the existence of abnormally reduced neuronal sensitivity leading to abnormal thresholds for novel stimuli can also be proposed. Few studies have looked for deficits in auditory performance in schizophrenia. Experiments using tonal audiometric procedures have shown that these abnormalities in auditory function appear in a context of normal auditory acuity, except that schizophrenic patients do not consistently show the usual auditory threshold asymmetry in favour of the right ear.¹⁷ In a more recent study, Mathew *et al* found a degradation in hearing thresholds in schizophrenic patients, with better right ear acuity only in the non-hallucinating patients.¹⁸ These data point to a loss of threshold asymmetry in one (hallucinating) subgroup of schizophrenic patients.

There is thus evidence from many sources that auditory input integration and perception are disturbed in schizophrenia. In auditory information processing, the signal undergoes encoding and initial filtering as early as the cochlea. In 1992, Dallos showed that the outer hair cells of the organ of Corti have a primordial role in encoding the signal which is to be received and processed by the inner hair cells and then transmitted by auditory nerve afferent neurons.¹⁹ These outer hair cells, in turn, are the target of medial olivocochlear neurons,²⁰ originating in the superior olivary complex.^{21,22} It has been shown in animals that electrical or acoustic stimulation of medial

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olivocochlear fibres alters the nervous message released in the afferent auditory fibre (see Guinan²³ for a review). There is increasing evidence that the efferent fibres of the olivocochlear bundle, by innervating the outer hair cells, can affect sensory processing at the periphery. In humans, this medial olivocochlear system can be easily explored by means of otoacoustic emissions, which are sounds of cochlear origin.²⁴ It is now generally accepted that the origin of otoacoustic emissions lies in the outer hair cells, which undergo active mechanical displacement through the action of the contractile elements, myosin and actin, contained in their infrastructure.^{25–26} In response to sound input, the outer hair cells change length, which causes cochlear vibration and which may in turn generate sound. A small fraction of this biological energy is retransmitted backwards in the form of a pressure wave to the tympanum via the oval window and ossicular chain. The consequent vibration of the tympanum generates a low level acoustic signal which can be detected with a sensitive microphone in the outer auditory canal.²⁷ There are different types of otoacoustic emission: the first major class consists of continuous narrow band signals around one or more frequencies which can be found in the absence of any deliberate acoustic stimulation. They are known as “spontaneous otoacoustic emissions”. Otoacoustic emissions can also occur as a broad band acoustic signal in response to an evoking click, and are then called “click evoked otoacoustic emissions”.²⁸ In humans, otoacoustic emissions are a unique tool for examining the cochlea, allowing direct non-invasive communication with the sensory cells. They are particularly sensitive in detecting hearing loss and the fact that they are absent in patients with hearing loss exceeding 25–30 dB HL (see Probst *et al.*²⁸ for a review) shows that otoacoustic emission generation is related to optimal functioning of the ear. Kemp²⁹ hypothesised that discontinuities in outer hair cell distribution modified the sound energy produced by otoacoustic emissions. Moreover, click evoked otoacoustic emissions have been found to decrease in amplitude when a noise is applied in the contralateral ear.^{30–31} Such an effect, in which an efferent pathway is able to affect cochlear mechanics, was initially described in animal experiments.^{32–33} Evidence for efferent involvement comes not only from animal,^{34–35} but also from human studies, in which it has been reported that this contralateral suppression of click evoked otoacoustic emission is absent or greatly reduced in patients with vestibular neurectomy.^{36–38} As this section concerns the efferent fibres, these findings provide one of the main arguments for medial olivocochlear system involvement in the contralateral suppression effect. The medial olivocochlear system is part of the regulatory complex which modulates or regulates cochlear activity and auditory afferent inputs, improving the detection of multitone complexes in noise.^{39–41} Abnormally reduced functioning of this system has been found in hyperacusia,⁴² and autism,⁴³ two diseases in which impaired auditory

processing is suspected, as is also the case in schizophrenia. Moreover, anatomical animal studies have shown neurophysiological connections between certain cortical areas and the superior olivary complex,⁴⁴ which raise the possibility of central control of this modulatory olivocochlear feedback. Recent studies have shown that the medial olivocochlear system shows a pattern of functional asymmetry which is influenced by handedness,^{45–46} and so could be the reflection of a central laterality.

These peripheral auditory mechanisms and their regulation by the CNS have never been studied in schizophrenia. The aim of the present study was therefore to compare cochlear mechanics and their central efferent suppression between schizophrenic patients and normal control subjects, with objective and non-invasive methods. As auditory abnormalities are reported to be more consistent in hallucinating than in non-hallucinating schizophrenic patients, we included only patients who reported auditory hallucinations.

Methods

SUBJECTS

Twenty four subjects were recruited for the study. All gave written consent. Exclusion criteria included history of medical or neurological illness or trauma. Twelve were schizophrenic patients (four outpatients and eight inpatients) who met DSM-IV diagnostic criteria⁴⁷ for chronic schizophrenia (duration of illness > 2 years) with a mean illness duration of 11.7 (SE 3.5) years (range 2–37 years) and a mean average age at symptom onset of 20.2 (SE 0.6) years (range 17–25 years). The clinical severity of the patients' illness was assessed by the brief psychiatric rating scale (BPRS),⁴⁸ the scale for assessment of negative symptoms (SANS),⁴⁹ and the scale for assessment of positive symptoms (SAPS).⁵⁰ There were five paranoid, two disorganised, and five undifferentiated schizophrenic patients, all reporting auditory hallucinations (score 4.0 (SE 0.4); range 2–6 years). At the time of testing, 10 patients were taking neuroleptic medication (mean daily medication dose in chlorpromazine-equivalents: 624 (SE 62.2) mg; range 380–950). Two patients had been free of any treatment for at least 4 weeks. Seven patients were also receiving antiparkinsonism treatment (tropatepine) with a mean dose of 14.3 mg (SE 2.0); range 10–20). All patients were clinically stable at the time of evaluation and testing. The 12 other subjects were normal controls with no history of psychiatric illness or neurological disorder. The mean ages of the two groups were statistically similar (31.9 (SE 3.6) (range 21–58 years) for the schizophrenic patients, and 29.5 (SE 3.3) (range 18–57 years) for the normal controls (Mann-Whitney *U* test $t=125.5$, $p=0.712$)). Eight men and four women were included in each group. On the Edinburgh handedness scale,⁵¹ all subjects were right handed with scores above 70. Mean scores were statistically comparable between groups (92.5% (SE 3.3); range 70–100) for the normal controls and 90.8% (SE 2.8); range 80–100) for the schizophrenic patients.

HEARING TESTS

The battery of four tests was typically administered in the following order:

Pure tone audiogram

Thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz were measured in a soundproof room using a Madsen DAIH audiometer. All the subjects included in this study had auditory threshold losses of less than 25 dB HL at all frequencies.

Tympanogram

Standard admittance screening was conducted using a manual tympanometer (Amplaid 702) to check the functional integrity of the middle ear. The threshold of the acoustic reflex to contralateral broadband noise was also measured. All the subjects included in the present study (normal controls and schizophrenic patients) had a stapedial reflex with threshold never below 80 dB SPL or above 100 dB SPL. The mean values obtained in the right and left ears did not differ significantly between the two groups.

Otoacoustic emission recordings and medial olivocochlear exploration

All the measures were made in a sound-attenuated chamber, using the ILO92 equipment (Otodynamics® software, version 3.94 L), described in detail elsewhere.⁵² The right ear and left ear were investigated in random order. The subjects were instructed to relax, lie quietly, and remain awake. A probe was sealed with a perforated foam tip in the outer ear canal. Click evoked otoacoustic emissions were obtained in response to a non-filtered click of 80 μ s duration, presented at a repetition rate of 50/s. Three hundred responses were averaged with a band pass of 500–6000 Hz. A first recording used the non-linear differential mode to obtain click evoked otoacoustic emission at a high stimulus intensity of around 83 (SE 3) dB SPL (sound pressure level) for a time window of between 2.6 and 20 ms. Spontaneous otoacoustic emissions were then looked for. Finally, the medial olivocochlear system was explored by recording click evoked otoacoustic emissions with and without contralateral acoustic stimulation, following a protocol described elsewhere.⁴² Click evoked otoacoustic emission recording conditions were the same as above, except that five stimulus intensities, ranging between 60 and 72 dB SPL in 3 dB steps, were applied in random order using the linear mode. For each intensity, one recording with and one recording without contralateral acoustic stimulation were successively made, in random order. Each response was windowed, blanking out the first 3.20 ms. The contralateral acoustic stimulation was a 30 dB SPL continuous broad band noise (band width 50–8000 Hz).

DATA PROCESSING

For each click evoked otoacoustic emission, a measure of total level (“echo”) was given in dB SPL. In spontaneous otoacoustic emission recordings, the presence or absence of a spectrum peak was noted. A peak was retained

if the signal to noise ratio exceeded 4 dB. The number of peaks/ear was also noted. For medial olivocochlear exploration, the procedure allowed the equivalent attenuation to be calculated. The equivalent attenuation allows the quantification of medial olivocochlear functioning, and it is defined as the decrease in the ipsilateral stimulus (dB) which causes the same reduction in click evoked otoacoustic emission amplitude as does a 30 dB SL contralateral acoustic stimulation.^{42–53} This calculation is made from the “echo” level presented at five intensities with and without contralateral acoustic stimulation (see above). The lateralisation of this contralateral suppression effect was quantified with an asymmetry index corresponding to the relative difference between equivalent attenuation for the right ear and equivalent attenuation for the left ear. A positive value indicates a better functioning of the medial olivocochlear system in the right ear and a negative value indicates a better functioning in the left ear.

STATISTICAL ANALYSIS

Analysis was performed with SigmaStat® software (Jandel Scientific). All data are expressed as mean (SE). The group effect, the ear effect, and the interaction of group and ear on total click evoked otoacoustic emission amplitude and equivalent attenuation were analyzed with two way repeated measures analysis of variance (RM ANOVA) on one factor. When the RM ANOVA was found to be significant at $p < 0.05$ (for either the two factors or the interaction), a multiple comparison procedure was performed (Tukey test) to test differences between groups. A t test was used to compare the asymmetry index between the two groups. Z Tests were used to compare proportions.

Results

OTOACOUSTIC EMISSIONS

Figure 1 A plots the mean values of click evoked otoacoustic emission response level (by group and ear). The two way RM ANOVA on click evoked otoacoustic emission total amplitude disclosed no effect of group but an ear effect ($F_{1,22} = 9.85$; $p = 0.005$). Post hoc analyses by Tukey test indicated that the click evoked otoacoustic emission amplitudes were significantly larger in the right ear than in the left ear ($p < 0.005$). The interaction effect between (group $\times$ ear) was significant ($F_{1,22} = 5.63$; $p = 0.027$). The post hoc Tukey test indicated that the difference between right ear and left ear reached significance only within the schizophrenic patient group ($p < 0.001$).

For spontaneous otoacoustic emissions in the normal control group, the percentage of subjects with right ear spontaneous otoacoustic emissions was comparable with that for left ear spontaneous otoacoustic emissions (50%). These percentages were not significantly different from those obtained for the schizophrenic patient group (58% in the right ear and 33% in the left ear). On the other hand, schizophrenic patients tended to present multiple spontaneous otoacoustic emissions more often than did normal controls (fig 1 B). Although spontane-

Figure 1 (A) Mean (SE) amplitude of click evoked otoacoustic emissions and (B) peak number of spontaneous otoacoustic emissions for the normal control subjects and schizophrenic patients. * $p < 0.05$.

ous otoacoustic emission peaks predominated in the right ear in both groups, the schizophrenic patients' right ear values tended to be higher. However, none of these differences reached significance.

Figure 2 Mean (SE) equivalent attenuation obtained in normal control subjects and schizophrenic patients for the right and left ears. * $p < 0.05$. The more negative the equivalent attenuation, the greater the contralateral suppression of click evoked otoacoustic emissions.

Figure 3 (A) Individual and (B) mean (SE) equivalent attenuation asymmetry index plotted according to group: normal controls and schizophrenic patients. A positive value indicates a right ear advantage and a negative value a left ear advantage. ** $p < 0.01$.

MOC MEASUREMENTS

Functioning

Figure 2 shows the mean absolute equivalent attenuation values for each group and ear. The contralateral suppressive effect was statistically comparable between groups, with a non-significant effect of group disclosed by two way RM ANOVA. There was, however, a significant effect of ear ($F_{1,22}=4.23$, $p=0.05$) and a significant interaction between group and ear ($F_{1,22}=10.13$, $p=0.004$). Post hoc Tukey tests indicated that the normal controls showed a significantly greater contralateral suppressive effect in the right than the left ear ($p < 0.001$), and such asymmetry was not found in the schizophrenic patient group.

Laterality

This absence of systematic lateral difference in schizophrenic patients, unlike normal controls, is illustrated in fig 3. When the individual data are considered (fig 3 A), it is seen that 10 out of 12 normal controls (83%) presented significantly greater right ear suppression—that is, a right ear advantage—whereas of schizophrenic patients only three (25%) showed such right ear advantage, eight presenting greater left ear suppression and one showing no laterality.

Mean asymmetry index values are plotted for both groups in fig 3 B. They were significantly different between the two groups (t test: $t=3.32$; $p < 0.003$) but only the mean value of the normal control group differed from 0 ($t=3.93$; $p < 0.001$).

Discussion

This study is the first direct objective comparison between normal controls and schizophrenic patients of functional peripheral auditory processing thought to be involved in the filtering of acoustic input. As expected, schizophrenic patients differed from normal controls, but the distinction was found only in comparisons related to laterality: in all other cases, no significant difference appeared between groups.

Schizophrenic patients had otoacoustic emission amplitudes comparable with those of the normal controls, with however, particularly high click evoked intensity and spontaneous otoacoustic emission number in the right ear. The literature mentions fluctuating but significant rises in hearing threshold, particularly in hallucinating schizophrenic patients, in whom the asymmetry in favour of the right ear is absent.¹⁸ As otoacoustic emissions test inner ear functional integrity, and degrade rapidly when hearing thresholds rise, there would seem to be a mismatch between our data, obtained with an objective test, and the findings of Mathew *et al*,¹⁸ obtained with a subjective test of hearing perception levels. There is, however, another possible interpretation. The presence of otoacoustic emissions is a reliable indicator of outer hair cell structural integrity. It can be hypothesised that higher click evoked otoacoustic emission amplitude and spontaneous otoacoustic emissions having multiple spectral peaks reflect an increase in cochlear amplification. Such a modification could affect nervous activity generated in the afferent, as found in animals,⁵⁴ disrupting the processing of information, and which could perhaps explain the degradation of hearing threshold described.¹⁸ Medial olivocochlear functioning was quantitatively similar between normal controls and schizophrenic patients, suggesting that the auditory dysfunction found in such patients is different from the impairment described in autistic children, in whom the medial olivocochlear system was found to be significantly less functional than in controls.⁴³ In fact, the main finding of the present study is that schizophrenic patients show an absence of normal functional medial olivocochlear asymmetry. Whereas mean medial olivocochlear functioning was better in the right ear of normal controls, confirming previous investigations,^{45, 46} right handed schizophrenic patients showed the kind of non-lateralised medial olivocochlear functioning seen in left handed normal controls.⁴⁶ This absence of medial olivocochlear function asymmetry cannot be linked to the increased click evoked otoacoustic emission intensity in the right ear.^{55, 56} It is now well established that the auditory pathways are crossed, so that acoustic signals perceived in the right ear are integrated by auditory areas located in the left temporal cortex. Moreover, the planum temporale, thought to play an important part in language, is larger in this left hemisphere for normal right handed subjects,^{57, 58} receives direct auditory projections from the medial geniculate body—the subcortical relay nucleus for the auditory afferent

system—and is probably involved in the early auditory processing.⁵⁹ There is strong evidence that schizophrenic patients, particularly those with auditory hallucinations, have reduced cerebral asymmetry in the region of the planum temporale (see Ross and Pearlson⁶⁰ for a review⁶¹). Thus, the absence of functional medial olivocochlear asymmetry found in schizophrenic patients may be attributed to an impairment of the central modulation influencing the auditory efferent pathways, and so reflects the reduced central auditory asymmetry in these cortical areas. Based on this hypothesis, the present study could support the notion that schizophrenia involves certain abnormalities in cerebral laterality.^{62–64} However, no significant difference in suppression was found between normal controls and schizophrenic patients and it was not possible here to determine on which side (right or left) the medial olivocochlear system was more impaired and on which it was more activated.

Atypical lateralisation of auditory function in schizophrenic patients compared with normal controls has also been reported for other functional measures such as right ear advantage in dichotic listening tests,^{65, 66} or P300,⁶⁷ which, being subjective procedures requiring active participation from subjects, are thought to involve attention processes which are greatly impaired in schizophrenia.⁶⁸ The strength of the present study is that all the procedures were objective, and subjects had no response to provide nor any cognitive task to perform. Our findings thus cannot be attributed to any alteration of attention processes, but rather identify, in a significant fraction of schizophrenic patients, disturbances indicating processing anomalies of auditory message perception as of peripheral level, which could in turn be related to anomalies in central lateralisation.

It is important to acknowledge several limitations of the present study. Firstly, there is the possible influence of the antipsychotic medication taken by most of the schizophrenic patients in this study. However, the primary effect of antipsychotic medication is an improvement in cognitive functions such as attention (see Green and King⁶⁹ for a review). This effect has been seen to be lateralised, advantaging left hemisphere attentional processes (see Gruzeliér⁷⁰ for a review). The present study, however, used a methodology which does not rely on subjects' conscious processing, thus limiting the influence of cognitive processing and of the attention component in particular. Moreover, our findings with patients under neuroleptic drugs tend to show an absence of lateralisation, which seems to further confirm the fact that this procedure does not involve such attentional processes. Hence, there is no particular evidence that the absence of right ear advantage in medial olivocochlear functioning could be attributable to any such medication effect. On the other hand, this persistent loss of asymmetry even under medication might constitute a state independent vulnerability marker, as it seems to be the case for the P300 abnormalities found in the auditory mode.

This is also an important argument against any significant impact of the second possible limitation of the present work, the existence of auditory hallucinations at test time, this factor being always difficult to quantify. For technical reasons, it must be underlined that the patients were always tested outside hallucinating periods.

Lastly, our study concerned peripheral auditory mechanisms only in schizophrenic patients who reported several times auditory hallucinations as compared with normal controls, and so does not provide data as to whether the abnormal peripheral auditory asymmetry in schizophrenia concerns psychosis in general, or is specific to schizophrenia itself, or indeed to auditory hallucinations. Further studies comparing subjects with psychotic depression, non-psychotic depression, and schizophrenia with and without auditory hallucinations seem to be warranted.

To summarise the present study is, to our knowledge, the first to explore objectively, in schizophrenia, certain functional auditory mechanisms thought to be under cerebral control, and provides a promising approach for the objective study of alterations in auditory perception in schizophrenia. This medial olivocochlear system lateralisation, which could be of importance in peripheral auditory filtering, could be an interesting "trait-like" cognitive marker in schizophrenia and its measurement might be usefully integrated in the functional exploration test battery, so as better to understand the auditory abnormalities which characterise some mental diseases such as schizophrenia. The present data suggest that additional studies on a larger sample are needed not only to improve the statistical power regarding non-significant findings but also to compare between subtypes.

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