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SCHIZOPHRENIA is associated with an absence of the lateralizations that typify the human brain. Previous evidence emphasized structural changes, particularly reduced asymmetry in extension and surface of the planum temporale, although gross structural deviations occur only in a minority of patients. The present study describes an absence of lateralization on a robust functional measure that characterized schizophrenia patients: healthy subjects but not schizophrenics displayed a contralateral left-hemispheric dominance of the auditory evoked magnetic field to right-ear auditory stimulation. Absence of contralateral dominance in response to auditory stimuli among schizophrenia patients may indicate a failure to establish unequivocal left-hemispheric dominance of the phonological loop as hypothesized by Crow.

Key words: Auditory evoked magnetic response; Lateral asymmetry; MEG; Schizophrenia

Failure of dominant left-hemispheric activation to right-ear stimulation in schizophrenia

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Introduction

With the exception of the olfactory pathway, afferent sensory input is mainly (the auditory, somatosensory and motor systems), or even exclusively (the visual system), received by the contralateral sensory cortex. Consequently, magnitude of the auditory magnetic field evoked by unilateral tone bursts is normally larger over the contralateral than over the ipsilateral side.[1] When tone bursts are presented in trains (e.g. 0. 5 Hz), the field variance of the neuromagnetic response near 10 0ms (N1m) is described by a single equivalent current dipole located in auditory cortex. In a previous study[2] we found that for right ear stimulation the contralateral dipole moment occurred earlier and was larger by about one-third over the contralateral left hemisphere than over the ipsilateral right hemisphere in a sample of six healthy subjects.

A reduction or even a reversal of asymmetry has been reported for schizophrenic patients, with evidence indicating reduced asymmetry in extension and surface of the planum temporale. Gross structural deviations, however, occur only in a minority of patients.[3–5] Nevertheless, these data suggest that neuropathology in cortical regions involved in auditory information processing may be associated with schizophrenia. According to Crow,[6–8] absence of contralateral dominance in response to auditory stimuli among schizophrenia patients may index a failure to establish unequivocal left-hemispheric dominance of the phonological loop, constituting a prerequisite for the development of schizophrenic symptoms. Functional measures of auditory processing abnormalities may, therefore, be more sensitive to this abnormality than assessment of structural deviations. To evaluate this possibility, the present study examined hemispheric lateralization of the auditory evoked magnetic field to right ear auditory stimulation in schizophrenic and normal subjects using a whole head neuromagnetometer.

Materials and Methods

Using the same method as that described by Pante *vet a l*,[2] we investigated 10 patients (three female) with a schizophrenic disorder (DSM-IV diagnoses 295.1 and 295.3) and 10 healthy subjects (five female). All subjects were right-handed as established by the Edinburgh Handedness questionnaire and had normal audiological status as established prior to the experimental session. The chronic (more than two admissions) patients (seven outpatients) were receiving maintenance doses of neuroleptic

medication. All subjects were informed about the experimental procedure and signed a written consent form.

In a passive listening task, four series of 128 tone bursts (500 ms duration; 10 ms rise and fall time, cosine function) each were delivered to the right ear at 60 dB nHL (above individually determined hearing level). The interstimulus interval was randomized between 2.7 and 3.3 s. Across series stimuli had a carrier frequency of 500, 1000, 2000 or 4000 Hz, the sequence of frequencies being randomized across subjects. Stimuli were presented through a non-magnetic and echo-free stimulus delivery system with an almost linear frequency characteristic (deviations less than ± 4 dB in the range 200–4000 Hz).

For the measurement a lying position was chosen as being more comfortable and ensuring that the subject did not move during the measurement. Subjects were asked to stay awake, to keep his/her eyes open, and to fixate the gaze onto a point on the chamber ceiling. Compliance was verified by video-monitoring throughout the measurement. The stability of the head-sensor position was controlled by repeated measurements of the known positions of five indicator coils fixed on the scalp.

Auditory magnetic fields evoked by the different stimuli were recorded simultaneously from the left and right hemisphere using a wholehead neuromagnetometer (MAGNES 2400, Biomagnetic Technologies) installed within a magnetically shielded chamber. The measuring surface of the sensor is helmet shaped and covers the entire cranium. Within the sensor 148 signal detectors (magnetometer-type) are arranged in a uniformly distributed array spaced by 28 mm.

Stimulus related epochs of 1000 ms (including a 200 ms prestimulus interval) were recorded with a bandwidth of 1–100 Hz and a sampling frequency of 387.5 Hz. The auditory event-related field (AEF) that was submitted to the source analysis resulted from an average of approximately 128 stimulus epochs. Epochs contaminated by muscle or eye blink artifacts with amplitude variations of more than 3 pT in any channel were automatically rejected from averaging. The baseline was corrected for each channel according to the mean value of the signal during the 100 ms prior to the stimulus (DC offset). For the analysis of the N100m response, evoked fields were filtered using a low-pass of 20 Hz (second order zero-base shift, Butterworth filter, 12 dB/oct) and a high-pass of 1 Hz. A single equivalent current dipole (ECD) in a best fitting local sphere was estimated separately for the left and the right hemisphere for each stimulus condition. Since the AEF generated in the left and the right hemisphere showed little overlap, subsets of about 40 channels that included the signal from either the left or the right auditory areas were selected for source analysis. An ECD defined by dipole moment, orientation and space coordinates was calculated for each sample point. The location of the ECD was estimated in a head-based coordinate system. The origin of this coordinate system was set at the midpoint of the medial–lateral axis (y-axis) which joined the center points of the entrance to the acoustic meatus of the left and the right ears (positive towards the left ear). The posterior–anterior axis (x-axis) was oriented from the origin to the nasion (positive towards the nasion) and the inferior–superior axis (z-axis) was perpendicular to the x-y plane (positive towards the vertex). Analysis of the data was concentrated on the major component of the AEF, the N100m. Each N100m dipole parameter was represented by the average of 12 data points (30 ms interval) around the maximum of the root square of the magnetic field calculated across the respective subset of channels. The calculated values were accepted for further analysis when they satisfied the following source analysis and anatomical requirements: goodness of fit of the ECD model to the measured field > 90%; confidence volume <300 mm^2, range of source coordinates within the 30 ms interval < 2 cm; anterior–posterior value within ± 3 cm; medial–lateral value (distance to the midsagittal plane) > 2.5 cm, inferior–superior value > 3 < 8 cm. The individual median was calculated across those stimulation frequencies that met the above listed requirements. The goodness of fit of the ECD model to the measured field, taken as indicator of the data quality, did not differ between groups ($F < 1$; $r = 0.978$ for the patients and 0.983 for the control group).

Results

Consistent with earlier findings[2,9,10] the N1m peak (averaged across frequencies) occurred at an earlier latency over the contralateral left than over the ipsilateral right hemisphere in both groups (mean ± s.e.) 112.1 ± 3.2 ms *vs* 119.7 ± 3.2 ms, $F(1,17) = 19.4$, $p < 0.001$). This was the only statistically significant effect on N1m peak latency. Both the raw signal power (see Fig. 1) (root mean square, RMS, across subsets of about 40 channels that included the signal from either the left or the right auditory areas[2]) and the modeled N1m dipole moment (Q) showed a larger left/contralateral than right/ipsilateral magnitude in controls. In contrast, such a dominance was not obvious in patients (interaction group × hemisphere: $F(1,18) = 17.8$, $p < 0.001$ for Q; $F(1,18) = 4.7$, $p = 0.05$ for RMS). When asymmetry was expressed as a laterality quotient (ipsilateral minus contralateral N1m divided by ipsilateral plus contralateral

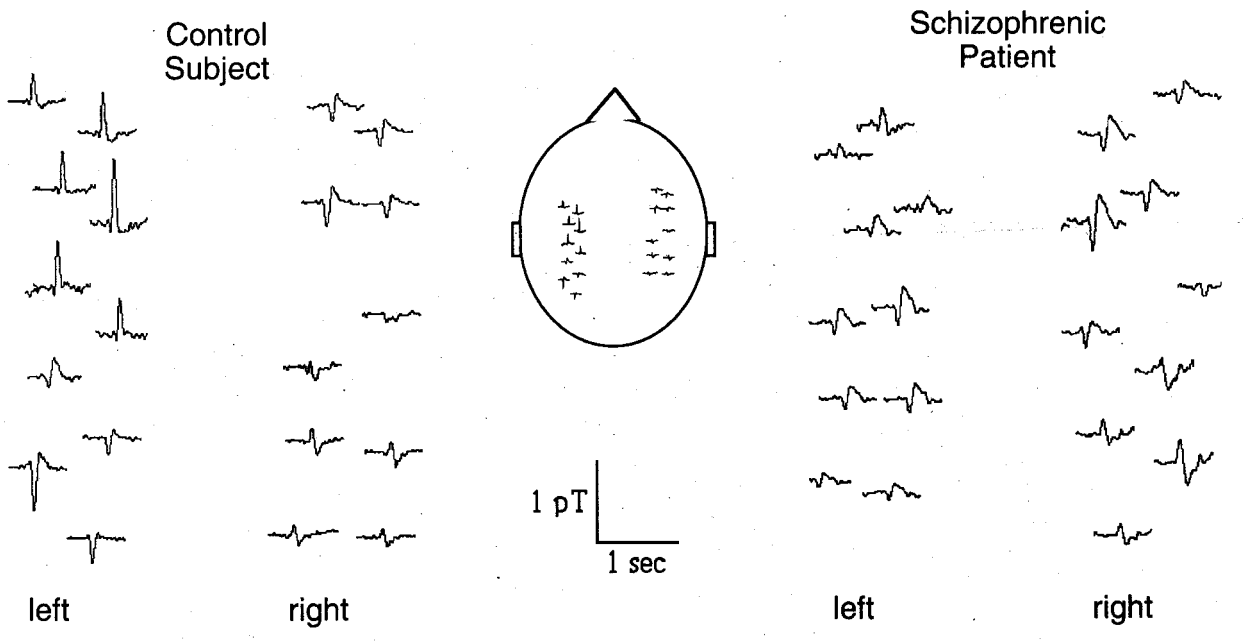

FIG. 1. Example of the auditory evoked magnetic response to 1000 Hz tones (averaged across 128 stimuli) presented monaurally to the right ear, obtained from a control subject (left) and a schizophrenic patient (right). The insert illustrates the approximate orientation of the selection of left and right hemispheric sensors.

N1m), the average asymmetry was −0.23 ± 0.6 for controls and +0.03 ± 0.04 for patients ($F(1,18) = 13.3$, $p < 0.001$; Fig. 2).

This effect could not be explained by differences in source localization between groups, as it was also apparent in the laterality quotient of raw MEG signal power ($F(1,18) = 6.8$, $p < 0.02$). Sources were located more anterior in the right (1.66 ± 0.2 cm) than the left (1.06 ± 0.2 cm) temporal lobe in both groups ($F(1,18) = 11.6$, $p < 0.01$), which is expected on the basis of structural differences.[5] Anterior/posterior source localization asymmetry, however, did not significantly differentiate controls (0.8 ± 0.3 cm) and patients (0.4 ± 0.2 cm, $F(1,18) = 1.3$, n.s). In both hemispheres, sources were more inferior by an average of 0.8 cm in patients than in controls ($p < 0.01$). There were no other statistically significant effects on source localization. Group differences in the asymmetry of auditory activation did not systematically vary with sex or age.

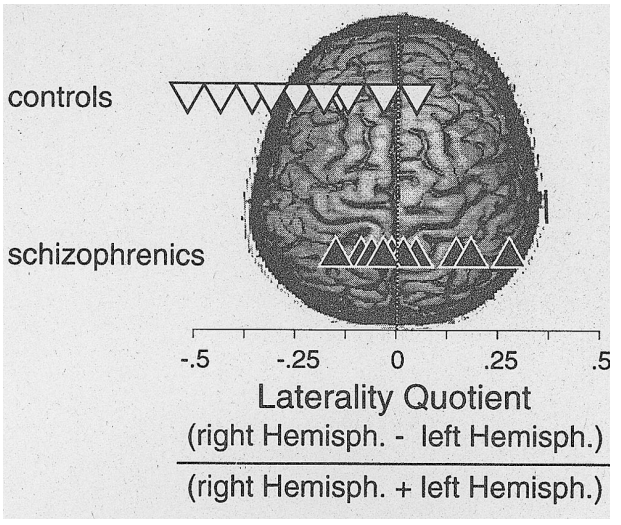

FIG. 2. Distribution of the N1m asymmetry determined as laterality quotient (difference of the respective right minus left hemispheric Q-values divided by their sum) for 10 healthy subjects (open triangles) and 10 schizophrenic patients (black triangles). The illustrative projection of the individual laterality quotients on a sketched cortical surface does not correspond to N100m dipole location as described in the text.

Discussion

Variations in normal brain asymmetries may be associated with a variety of neuropathologies. It has often been argued that temporal lobe asymmetries may underlie language-related hemispheric specialization. Theoretically, deviations from this asymmetry and alterations in interhemispheric communication are related to the emergence of schizophrenic symptoms.[6–8] Crow suggested that failure to establish unequivocal hemispheric dominance is associated with psychotic symptom development. Lack of contralateral dominance in the auditory pathway, as reported here for schizophrenia patients, may index a failure to develop language-related hemispheric specialization.

The observed functional symmetry in schizophrenia patients might result from individual anatomical variations in the auditory pathway. For example, in the somatosensory system, about 1% of the population deviates from normal contralateral dominance. Perhaps the extent of contralateral dominance in the auditory pathway of schizophrenia patients is altered from normal. Alternatively, schizophrenia patients' lack of auditory asymmetry may result from failure of contralateral afferents to inhibit the ipsilateral pathway. This possibility seems less likely, as results indicate reduced contralateral rather than enhanced ipsilateral responses. A third alternative could be that the observed symmetry in schizophrenic patients is not the cause but the consequence of symmetric processing of language that is more prominent in schizophrenia. The auditory channel carries most of the relevant language information. Symmetrical organization of language may trigger a use-dependent functional reorganization of auditory cortex such that the afferent input to one ear is equally well received by both hemispheres. It is important to test the latter notion because it suggests interventions that may reduce schizophrenic symptoms by taking advantage of the brain's capacity for massive functional reorganization.

Atypical lateralization of auditory function in schizophrenic patients compared with controls has also been reported for other functional measures such as right-ear advantage in dichotic listening[11] or auditory P300,[12] or the postimperative response following ambiguous delayed matching.[13] Thus it seems that normal brain asymmetry, measured in a variety of ways, becomes blurred at least in a significant fraction of schizophrenic patients. Deviances from the normal fetal[14] development of brain cytoarchitecture and asymmetry of function are discussed as a consequence of neurodevelopmental defects, i.e. static lesions during the second trimester, that become manifest when frontal and temporal cortices reach functional maturity in early adulthood,[15,16] or as a consequence of slower maturation.[17] In addition, structural or functional damage to the brain, such as microlesions, focal dysfunctions (caused by traumatic experience), or alterations in neurotransmission, might trigger plastic alterations in the brain's functional organization whereby homologous areas in the intact hemisphere might compensate for loss of function on the lesioned side.[18,19] From that perspective, blurred asymmetry should constitute an observable outcome.

Conclusion

Absence of left-hemispheric contralateral dominance in response to right-ear auditory stimuli among schizophrenia patients may index a failure to establish normal development of brain asymmetry. The present results confirm absence of lateralization for a functional measure, the auditory magnetic N100.

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