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Functional MR Spectroscopy of the Auditory Cortex in Healthy Subjects and Patients with Sudden Hearing Loss

T. L. Richards, G. A. Gates, J. C. Gardner, T. Merrill, C. E. Hayes, H. Panagiotides, S. Serafini, and E. W. Rubel

PURPOSE: To use MR spectroscopy to study the biochemical changes produced by auditory stimuli in patients with sudden sensorineural hearing loss and to compare these findings with the biochemical changes seen in healthy volunteers. **METHODS:** Single-voxel MR spectroscopy was used to study biochemical changes in the auditory cortex in 11 control subjects and 19 patients with sudden sensorineural hearing loss. MR spectroscopic signals were measured during three different sound conditions (scanner noise, music, and sirens). **RESULTS:** A lower MR spectroscopic lactate signal was observed in control subjects during the music stimulus than during the other sound conditions. This music-induced lactate change was not observed in the patients with hearing loss. The other proton metabolites (choline, creatine, *N*-acetylaspartate [NAA]) remained stable during the different auditory stimuli. However, the NAA/creatine ratio was higher in the auditory cortex of patients than in the control subjects, and was not dependent on the sound condition. **CONCLUSION:** The detection of stimulus-induced and stable biochemical MR spectroscopic changes in patients with hearing loss may be useful in assessing disease activity.

Index terms: Magnetic resonance, spectroscopy; Hearing

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Sudden sensorineural hearing loss is a fairly common clinical syndrome in which patients lose useful hearing over a few minutes to hours (1). The vast majority of cases involve only one ear and about 40% are associated with vertigo. About one third of the patients recover fully, one third improve somewhat, and one third show no improvement. Efforts to develop a reasonable treatment have been hampered by the absence of clinical markers that might indicate disease pathogenesis. Current theories suggest that reversible cases involve reduction in cochlear blood flow at the microvascular level, whereas nonreversible cases may be caused by viral infection, particularly when accompanied by vertigo.

Magnetic resonance (MR) imaging with MR spectroscopy is a relatively new technique that permits in vivo detection of *N*-acetylaspartate (NAA) (a marker for neuronal damage and chronic brain damage) (2–4), choline (Cho) (a marker for disturbances in membrane metabolism) (5–7), creatine (Cr) plus phosphocreatine (both chemicals are involved in phosphoenergetics), and lactic acid (a marker for brain activation) (8, 9). Functional MR spectroscopic studies of hearing loss disorders would be important in understanding how the proton metabolites listed above are affected in auditory pathways of the brain during neuronal activity.

The purpose of this investigation was to evaluate auditory stimulus-dependent and stimulus-independent MR spectroscopic biochemical changes in patients with sudden sensorineural hearing loss as compared with healthy volunteers. Our hypothesis was that hearing loss would be associated with a decrease in the ability of the auditory cortex to respond transiently to stimuli biochemically and also that there

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would be long-term biochemical changes in the neurons as they are deprived of stimulation.

Subjects and Methods

All otolaryngologists in the Puget Sound area were asked to have patients with severe, acute, unilateral sudden sensorineural hearing loss complete a patient registration form and to provide their clinical data to the study center. Patients were offered the opportunity to undergo additional testing. This included auditory brain stem response audiometry, distortion-product otoacoustic emission audiometry, phased-array MR imaging of the cochlea and cochlear nerve, and MR spectroscopy of the auditory cortex. Volunteer patients were accepted for scanning and objective testing if the onset of hearing loss was less than 30 days earlier, there was no history of hearing loss, the hearing loss was severe, and there was no evidence of trauma or middle ear infection. Treatment was not part of the protocol.

MR Spectroscopy

Volume-localized proton spectroscopy was measured in the right and left auditory cortex of 11 healthy volunteers and 19 patients with sudden sensorineural hearing loss. All 19 were invited to return for a repeat MR spectroscopic study but only 13 agreed to return 1 month after the first examination. The repeat visit was required to assess evolution in clinical signs and symptoms and in MR spectroscopic metabolites. MR imaging and spectroscopy were performed with a 1.5-T system. A specially designed bilateral temporal lobe, phased-array radio frequency (RF) coil (10) was used to improve the signal-to-noise ratio at the auditory cortex. The coil consisted of four separate elements (two on each side) contained in a flexible holder that wrapped along the overlying skin surface so that the coil elements could be placed as close as possible to the region of interest. Coronal MR images, fast spin-echo, 3-mm-thick sections, 3000/80 (repetition time/echo time), were obtained to find the coordinates of the left- and right-sided auditory cortex.

Spectroscopy was performed using the point-resolved spectroscopy (P. A. Bottomley, Selective Volume Method for Performing Localized NMR Spectroscopy, US Patent 4 480 228, 1984) pulse sequence (2000/272) with an 8 cm^3 voxel size. All spectra were prescanned with automatic software (General Electric, Milwaukee, Wis), which adjusts the RF transmit power, the RF frequency, the magnetic field homogeneity, and the RF power of water-suppression pulses. For raw MR signal quantification, the RF receiver gain was held constant and the RF power was adjusted to give a 90° pulse in the region of interest. Total acquisition time was 5 minutes after spectroscopy autoprescan. Resonance areas for Cho (3.2 ppm), Cr (3.0 ppm), NAA (2.0 ppm), and lactate (1.3 ppm) were measured by using lorentzian/gaussian curve fitting and baseline correction software developed in our laboratory. The MR resonance area was evaluated both as a raw signal (not as a ratio) and as a ratio to Cr: NAA/Cr, Cho/Cr, and lactate/Cr. The lactate peak was identified on the basis of its MR frequency (near 1.3 ppm) and the doublet nature of the resonance. An echo time of 272 milliseconds was chosen to obtain a spectrum in which both resonances of the lactate doublet were in phase and also to obtain a spectrum in which there was minimal contamination from lipids (which have a much shorter T2 relaxation time). An echo time of 136 milliseconds was used in two selected cases to verify that the lactate peak inverted.

Auditory Stimuli

Stimuli were delivered to subjects bilaterally using a GE Sound System, Model 3-5667. A funnel was sealed around each speaker of the sound system and secured to tubing (Fisher Scientific, Pittsburgh, Pa). This tubing was fed into an opening on both the left and right side of the phased-array RF head coils adjacent to the entrance of each ear canal to provide dichotic listening conditions. Spectroscopy was acquired during 5-minute auditory stimulation sessions with either no extra sound (ambient scanner gradient noise only); music (a jazz-style piano piece called "Solid Colors" by Liz Story from the Windham Hill Collection); or siren noises with the frequency range constantly changing to avoid habituation. The scanner noise could be heard during the presentation of all stimuli. All patients received all three stimuli during both left- and right-sided auditory cortex MR spectroscopic measurements. However, only five of the 11 healthy volunteers received all three sound stimuli. The other six received only the scanner noise and music stimuli (at the beginning of the study the siren stimulus had not yet been developed). Frequency and amplitude characterization of auditory stimuli were made inside the scanner room, using an ER-7C probe tube microphone (Etymotic Research, Inc, Elk Grove Village, Ill) and an HP-3561A Dynamic Signal Analyzer (Hewlett-Packard, Everett, Wash). Files from the HP were then downloaded to a Macintosh computer for analysis. During the sound characterization, the probe tube of the ER-7C microphone was secured on the inside portion of the left side of the head coil, where the tubing of the sound delivery system met the entrance to the ear canal. Owing to small variations in the subjects' head sizes and head coil fit, measurements were averaged over three different subjects. The signal analyzer was used to store 30-second samples of both stimuli and ambient scanner noise for peak and averaged sound amplitudes over a frequency range of 0 to 10 kHz.

Auditory Stimuli Characterization

The results of the auditory stimuli characterization are shown in Figure 1. The graph shows that the sound level of the music stimulus was an average of 13.5 dB higher than the scanner noise alone in the frequency region of 0 to 1230 Hz and that the music was an average of 11.4 dB higher in the 1230 to 10 kHz region than that of the scanner noise alone. The sound level of the siren stimulus

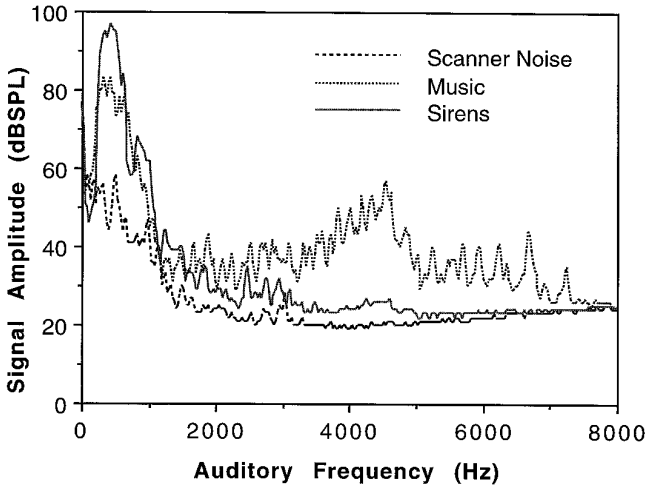

Fig 1. Plot of auditory signal amplitude as a function of frequency. The auditory signal was measured with a microphone in the RF coil during auditory stimulation with scanner noise alone, music plus scanner noise, and sirens plus scanner noise. The data show that the music and sirens are louder than the scanner noise at most frequencies; however, there is an inflexion point in the data where the music and sirens switch position in their order of signal amplitude.

was an average of 16.3 dB higher in the first frequency region and 2.1 dB higher in the second frequency region than that of the scanner noise alone.

Data Analysis and Statistics

One of the hypotheses tested in this study was that the auditory cortex would respond differently biochemically in patients with hearing loss than in healthy control subjects. This hypothesis was tested by means of a repeated measures analysis of variance using the SAS statistical software package (SAS Institute, Cary, NC). To test for differences in the MR spectroscopic metabolite levels produced by the different sound conditions among the subject groups, a global analysis of variance was used to test the entire data set followed by individual comparisons between pairs of sound conditions (eg, scanner noise versus music). A Tukey (multicomparison) test was performed for a between–subject group analysis to test for MR spectroscopic differences between the following subject groups: control subjects; patients during the first visit with hearing deficit in the left ear; patients during the first visit with hearing deficit in the right ear; patients during the second visit with hearing deficit in the left ear; and patients during the second visit with hearing deficit in the right ear. To quantitate the MR spectroscopic lactate response to auditory stimulation, a lactate hearing response quotient (LHRQ) was calculated using the following formula: LHRQ = (MR spectroscopy $\text{lactate}_{\text{music}}$ − MR spectroscopy $\text{lactate}_{\text{noise}}$)/MR spectroscopy $\text{lactate}_{\text{noise}}$. This quotient is an index of the MR spectroscopic changes in lactate level between scanner noise and music conditions and is a biochemical measure of the auditory cortex's ability to transiently change from one sound condition to the other. As defined by this equation, zero means no response and a negative number means that scanner noise resulted in a higher lactate signal than music. The LHRQ was also statistically tested for differences between control subjects and patient during the first visit and patients during the second visit by using the Tukey multicomparison test.

Results

Auditory Findings

All patients had a unilateral sensorineural hearing loss that was characterized as cochlear in site of origin by distortion-product otoacoustic emission and results of auditory brain stem response testing. The hearing loss was in the right ear in six (32%) of the patients and bore no relation to handedness or sex. The audiometric profile was generally downsloping. The pure-tone average (0.5, 1.0, and 2.0 kHz) was 105 dB hearing level for patients with right ear losses and 69 dB hearing level for patients with left ear losses, with a pure-tone average of 80.4 dB in the worse ear. On follow-up audiometry 1 or more months after the onset, six patients (32%) had improvement of more than 10 dB in their pure-tone average, with an average gain of 43 dB hearing level. The remainder had no appreciable change in their hearing. Vertigo was present in 10 cases (53%) but did not affect the hearing outcome. All patients received medical therapy (not part of the protocol), principally a short course of corticosteroids.

MR Spectroscopic Results

The MR spectroscopic measurements in both control subjects and patients contained detectable signal resonances from Cho, Cr, NAA, and lactate. An MR spectrum from a control subject is shown in Figure 2.

Auditory Stimulation and the MR Spectroscopic Response in Control Subjects

The averaged MR spectroscopic measurements from control subjects are shown in Table 1. For the control group, the MR spectroscopic lactate level (as measured by the resonance area) during the presentation of music (sound condition 2) was significantly lower than during the presentation of scanner noise (sound con-

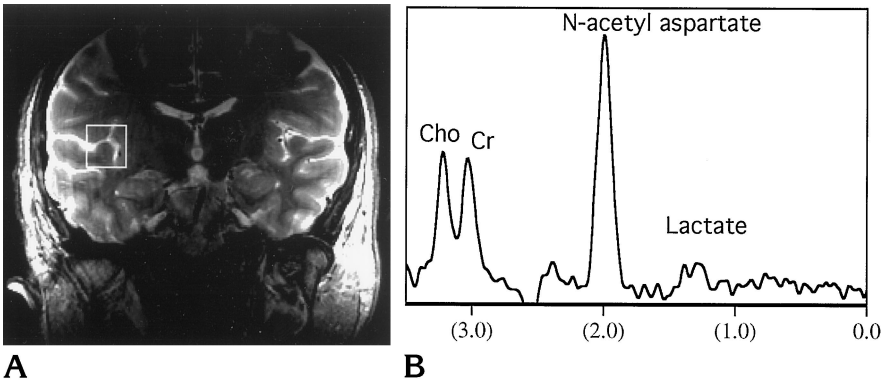

Fig 2. Coronal MR image (*A*) and MR spectrum of the right auditory cortex (*B*) of a healthy volunteer. The MR image was acquired using a fast spin-echo MR pulse sequence with parameters of 3000/80/1. The *box* over the left auditory cortex indicates the brain region measured with MR spectroscopy. The MR signal intensity drops off toward the center of the brain because of the RF homogeneity profile of the phased-array RF coils. The MR spectrum on the right indicates the biochemicals that are detectable with the parameters 2000/272/128. This spectrum was acquired from a 2 × 2 × 2-cm^3 brain region using the point-resolved spectroscopy pulse sequence.

TABLE 1: Normal MR spectroscopic values of the auditory cortex in response to three stimuli

	NAA/Cr	Cho/Cr	Lactate/Cr	n
L cortex				
Scanner noise	1.94 ± 0.18	1.06 ± 0.13	0.24 ± 0.07	10
Music	2.02 ± 0.16	1.06 ± 0.13	0.19 ± 0.06*	11
Sirens	1.84 ± 0.21	1.07 ± 0.11	0.23 ± 0.12	5
R cortex				
Scanner noise	2.26 ± 0.19	1.04 ± 0.17	0.31 ± 0.10	7
Music	2.14 ± 0.17	1.06 ± 0.09	0.24 ± 0.05	7
Sirens	2.19 ± 0.24	0.98 ± 0.13	0.30 ± 0.09	5

* Statistically significant difference ($P < .05$) from the scanner noise value.

Note.—The MR spectroscopic peak area ratios are displayed plus or minus standard deviation. NAA indicates *N*-acetylaspartate; Cho, choline; and Cr, creatine.

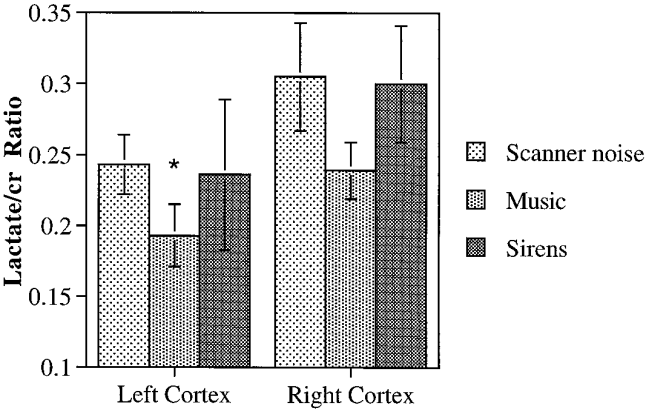

Fig 3. Averaged lactate/Cr ratio plotted for the left and right cortices during all three sound conditions for control subjects. The standard errors of the mean are displayed as error bars. The *asterisk* indicates a significant change in lactate in response to music as compared with that in response to scanner noise.

dition 1) in the left auditory cortex ($P < .004$, n = 10) as shown in Figure 3. Although this same comparison was not significant in the right cortex alone (because of the low number of MR spectroscopic measurements on the right side), five of the six control subjects had a lower MR spectroscopic lactate level during music than during the scanner noise. A set of MR spectroscopic spectra from a control subject (Fig 4) shows the lactate level is lower during music (right cortex). Also for the control group, the right cortex had a significantly higher lactate/Cr ratio ($P < .01$) and NAA/Cr ratio ($P < .001$) compared with the left cortex. MR spectroscopic lactate was the only metabolite that showed a significant change during the different sound conditions within each subject group. There were no significant changes in any of the other proton MR spectroscopic metabolites (NAA, Cr, Cho) in response to the three sound stimuli.

Auditory Stimulation and the MR Spectroscopic Response in Patients with Hearing Loss

The LHRQ was significantly higher in patients with hearing loss than in control subjects in both the contralateral and ipsilateral cortex (Fig 5A) during the first visit. The positive LHRQ value measured during the first visit (Fig 5A) means that the lactate level was higher in response to the music than in response to the scanner noise. During the second visit, the lactate level did not change significantly during the three different sound conditions, and the LHRQ was not signif-

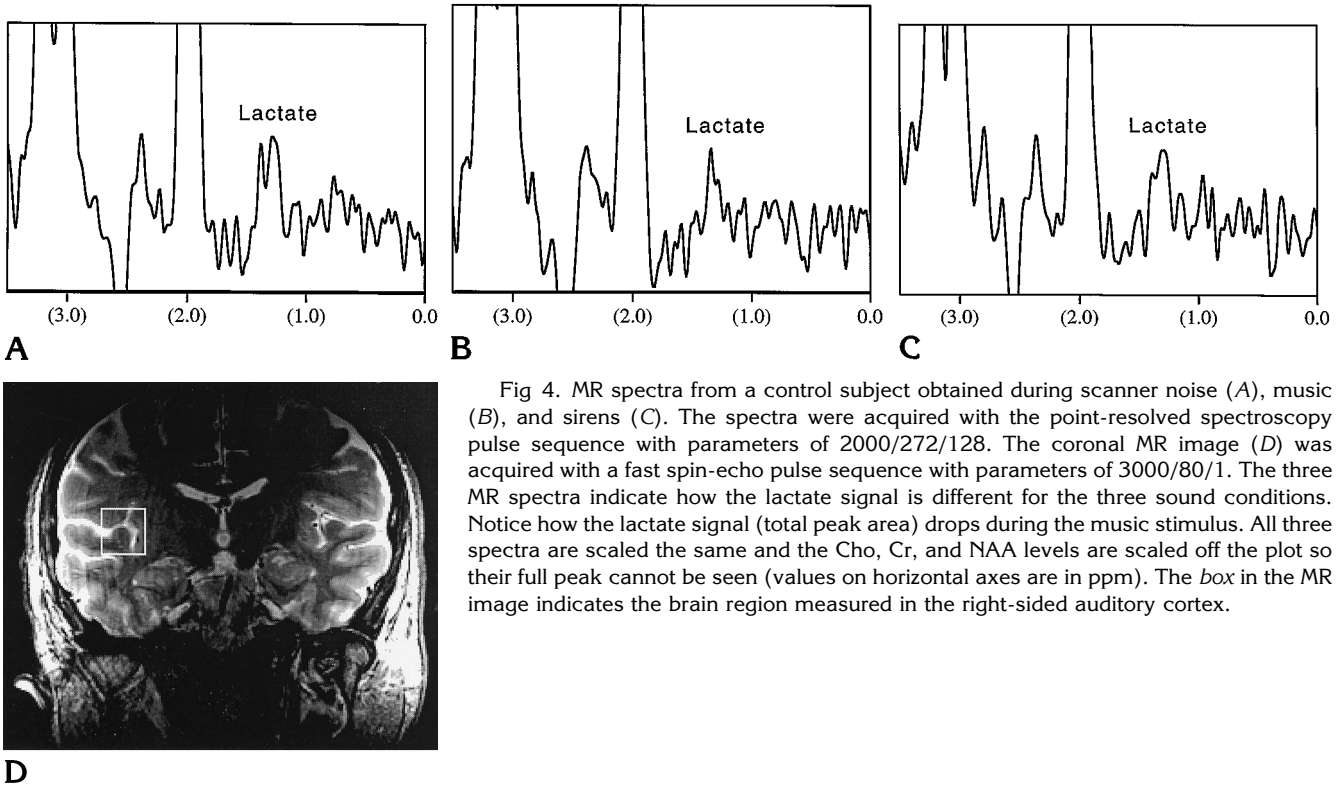

Fig 4. MR spectra from a control subject obtained during scanner noise (*A*), music (*B*), and sirens (*C*). The spectra were acquired with the point-resolved spectroscopy pulse sequence with parameters of 2000/272/128. The coronal MR image (*D*) was acquired with a fast spin-echo pulse sequence with parameters of 3000/80/1. The three MR spectra indicate how the lactate signal is different for the three sound conditions. Notice how the lactate signal (total peak area) drops during the music stimulus. All three spectra are scaled the same and the Cho, Cr, and NAA levels are scaled off the plot so their full peak cannot be seen (values on horizontal axes are in ppm). The *box* in the MR image indicates the brain region measured in the right-sided auditory cortex.

icantly different from zero (Fig 5A). There were no significant changes in any of the other proton MR spectroscopic metabolites (NAA, Cr, Cho) in response to the three sound stimuli (Fig 5B–D).

Overall MR Spectroscopic Results (Auditory Stimuli Independent Changes)

To calculate overall MR spectroscopic results, the MR spectroscopic ratios (NAA/Cr, lactate/Cr, Cho/Cr) and MR spectroscopic raw signals (NAA, Cr) were averaged over the sound conditions and sorted by the side of deafness. In the contralateral cortex, the NAA/Cr ratio was significantly higher in patients during the first visit than in control subjects (Fig 6A). The NAA peak areas (raw signal) shown in Figure 7A have generally the same pattern shown in Figure 6A and show that the average NAA area is higher (although not significantly so) in hearing loss patients than in control subjects. The Cr peak areas in Figure 7B show very little change between patients and control subjects. An example set of spectra is shown in Figure 8 to demonstrate the increased NAA/Cr ratio in the hearing loss patients. The lactate/Cr and Cho/Cr ratios for patients were not significantly different from those of control subjects (Fig 6B and C). The NAA/Cr ratio was also analyzed for abnormally high individual values, where abnormal was defined as two standard deviations from the control group average. Seven patients had abnormally high NAA/Cr ratios on both sides of the brain during the first visit (Table 2). The number of abnormally high NAA/Cr values decreased on the second visit compared with the first visit (Table 2). There were no significant differences in the Cho/Cr ratio between control subjects and patients on either the first or second visit (Fig 6).

Paired Tests Comparing the First and Second Visits

The lactate/Cr ratio was significantly higher ($P < .05$) during the first visit than during the second visit in the ipsilateral cortex for the music sound condition. The overall NAA/Cr ratio was significantly higher ($P < .05$) in the left cortex during the first visit than during the second visit in the patients with deafness in the left ear.

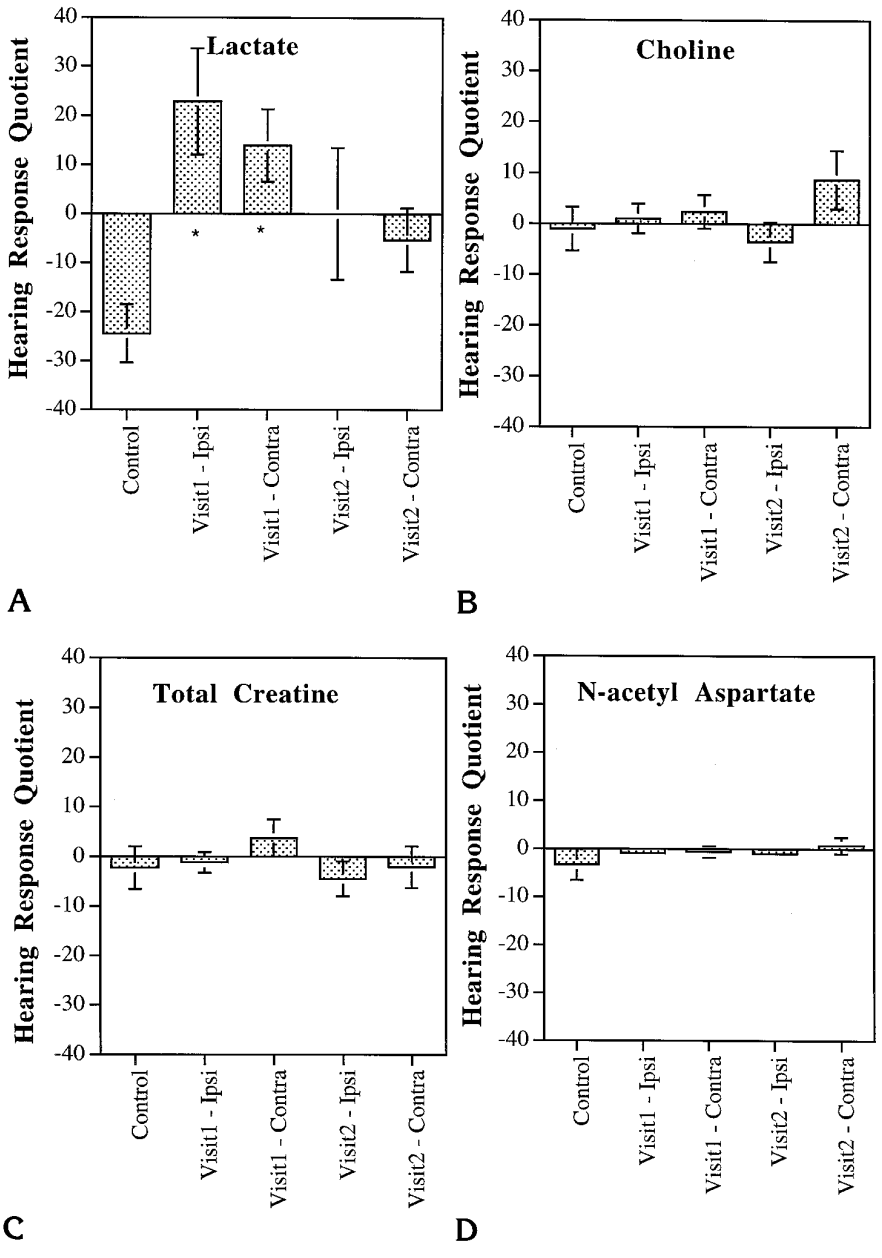

Fig 5. *A*, Lactate hearing response quotient (LHRQ) of the auditory cortex plotted as a function of study groups. Ipsilateral and contralateral refer to the LHRQ data from the ipsilateral and contralateral auditory cortex with respect to the side of the deaf ear. The LHRQ was calculated from the following equation: LHRQ = (lactate$_{music}$ − lactate$_{noise}$)/lactate$_{noise}$. *Asterisks* indicate significant difference from control value.

MR spectroscopic hearing response quotient from the auditory cortex for Cho (*B*), Cr (*C*), and NAA (*D*).

Discussion

MR Spectroscopic Lactate Effects

Brain activation in the cerebral cortex is influenced by both external stimuli and internal control (attention to stimulus). Increases in lactate have been observed in the occipital cortex (8, 9) and in the auditory cortex during 1-kHz tone pulses (11). The increase in lactate is thought to be related to an increase in glucose metabolism during neuronal stimulation. In a recent article by Tsacopoulos and Magistretti (12) it was implied that lactate is the preferred substrate for the tricarboxylic acid cycle in neurons. Using a model of metabolic compartmentation, these authors described glucose as being taken up by astrocytes and converted to lactate, which is then released in the extracellular space and used by neurons (12). Their model provides a cellular and molecular basis for interpreting the increase in MR spectroscopic lactate observed during brain activation, in which glycolysis may exceed the rate of oxidative phosphorylation and cause a transient increase in lactate levels.

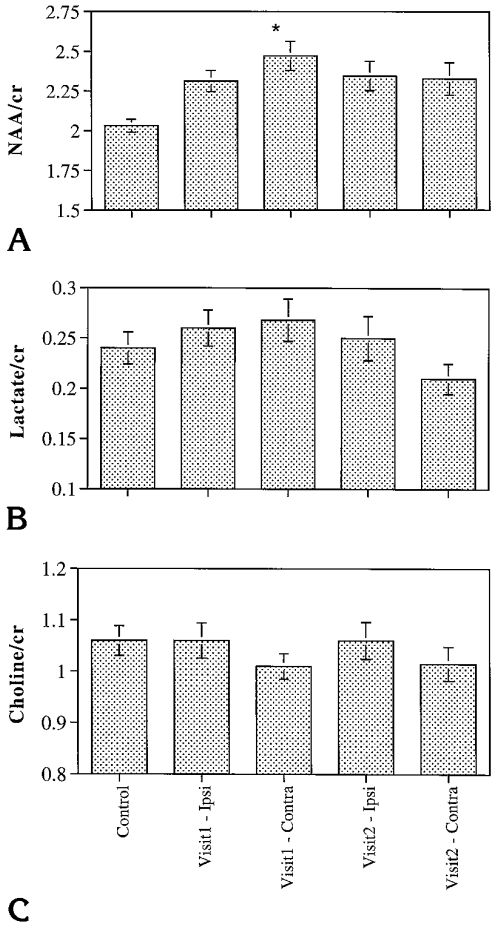

Fig 6. *A*, Average NAA/Cr ratio plotted as a function of subject group for the auditory cortex. The MR spectroscopic ratios were averaged over the sound conditions and over subjects within each subject group. Ipsilateral refers to the NAA/Cr data from the ipsilateral auditory cortex with respect to the side of the deaf ear. The error bars are displayed as standard error of the mean. *Asterisk* indicates significant difference from control value as measured with the Tukey multicomparison test.

Lactate/Cr ratio (*B*) and Cho/Cr ratio (*C*) plotted as a function of subject group.

Music Effects

The data generated in this study provide evidence that music reduces the lactate accumulation during brain activation (in control subjects) even when superimposed on other stimuli (gradient clicking noise). Perceptual and emotional musical experiences led to changes in blood pressure, pulse rate, respiration, psychogalvanic reflex, and other autonomic functions (13). These physiological effects are dependent on both the type of music and the musical training of the subject. Brain-wave topography has shown a predominance of activity on one or another side of the brain that varies as subjects listen to music produced by various instruments (14). Using positron emission tomography, Mazziotta et al (15) showed that monaural stimulation with musical chords caused bilateral parietotemporal activation and diffuse frontotemporal asymmetries, with the right side greater than the left. Our data are consistent with the work of Creutzfeldt and Ojemann (16), in which a decrease in neuronal activation (as measured by cortical electrical recordings) was measured from both temporal lobes during stimulation with piano music. These authors hypothesized that the decreased electrical activity during music may be due to an increased activation of inhibitory neuronal mechanisms. The decrease in lactate during the music condition could be explained by either the decreased neuronal activity within the volume of interest and/or by an increased perfusion of the cortex in the same volume of interest. The increased perfusion could decrease the concentration of brain lactate if the lactate produced in the neurons freely diffused from the intracellular to the extracellular compartment. The patients with hearing loss responded differently to the music than did the control subjects in that the average lactate levels during music were greater than during scanner noise on both sides of the brain. This lack of a relaxing effect from music in the patients with hearing loss may be due to a disruption in the neuronal signals from the deaf ear.

We found many ipsilateral and contralateral MR spectroscopic lactate and NAA effects in the auditory cortex. In comparing the MR spectroscopic data between the ipsilateral and contralateral cortices, we recognized many factors that could influence the metabolic levels: 1) asymmetries in the cerebral cortical activation during music stimulation (14); 2) variable responses to the same music stimulus, depending on how the subject perceives the music (13, 14); 3) deafness even in just one ear, which can interfere with the arrival of neuronal signals at both cerebral hemispheres; and 4) the tremendous amount of cross-talk that occurs between the two cerebral hemispheres via the corpus callosum during the 5 minute data acquisition time. According to a report by Popper and Eccles (17), the pathway from the cochlea to the primary auditory region (Heschl gyrus) has dominant contralateral pathways and less active ipsilateral pathways; however, the auditory cortex does receive input from both ears. The

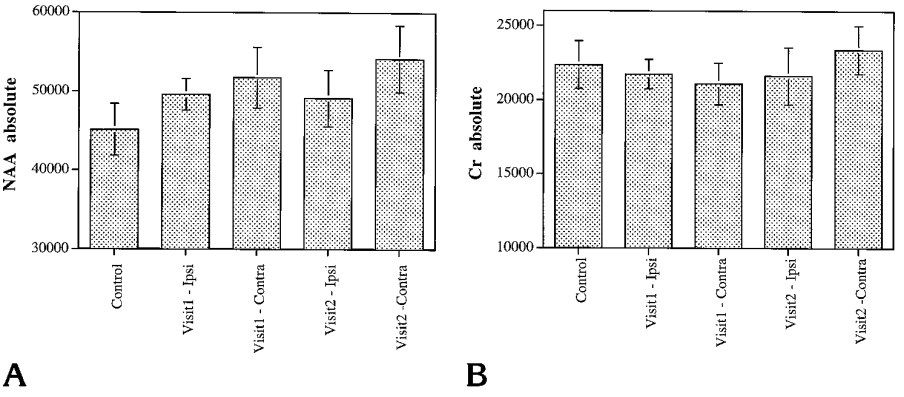

Fig 7. *A*, Average absolute NAA plotted as a function of subject group for the auditory cortex. The MR spectroscopic ratios were averaged over the sound conditions and over subjects within each subject group. Ipsilateral refers to the NAA data from the ipsilateral auditory cortex with respect to the side of the deaf ear. The error bars are displayed as standard error of the mean.

B, Absolute creatine plotted as a function of subject group.

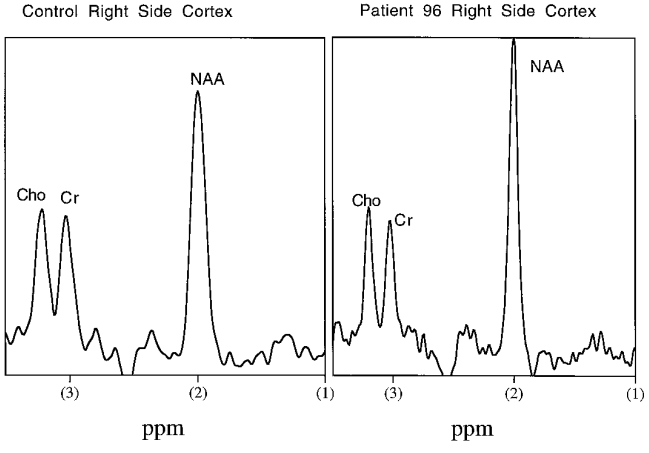

Fig 8. MR spectra from a healthy control subject (*left*) and from a patient with hearing loss (*right*) plotted side by side to show the increase in the NAA/Cr ratio in the patient. The spectra were acquired with the point-resolved spectroscopy pulse sequence with parameters of 2000/272/128. Both spectra are scaled with the Cr peak height for normalization.

TABLE 2: Number of patients in the first and second visits with a normal or abnormal NAA/Cr ratio

	Normal NAA/Cr	Abnormally High NAA/Cr
First visit		
Contralateral	5	14*
Ipsilateral	8	11
Both sides	...	7
Second visit		
Contralateral	11	8
Ipsilateral	11	8
Both sides	...	6

Note.—Abnormally high NAA/Cr is defined as 2 standard deviations higher than the average of the control group. NAA indicates *N*-acetylaspartate; Cr, creatine.

* Significant χ^2 ($P < .05$) for testing the effect of visit in a 2×2 contingency table. This result shows a significantly higher number of abnormally high NAA/Cr ratios during visit 1 compared with visit 2.

data from Table 2 also indicate that in our study both sides of the brain had abnormally high NAA/Cr ratios even though, in theory, the contralateral side should have had the greatest change.

MR Spectroscopic NAA Effects

The NAA, Cho, and Cr MR spectroscopic signals did not change significantly with auditory stimulation. However, there was a significant increase in the NAA/Cr ratio in the patients with hearing loss as compared with the control subjects that was independent of auditory stimulation. The changes in the NAA/Cr ratio may be related to the general disease conditions rather than to the specific sound stimulus. The average NAA areas (raw signal) were higher (although not significantly so) in patients than in the volunteers and therefore it is likely that the NAA/Cr increase in patients was due to an increase in NAA rather than to a decrease in Cr. The reason the NAA signal in patients was not significant was probably related to the greater variation in signal due to RF inhomogeneity. The NAA/Cr ratio was significant and may have been normalized better within subject groups because both NAA and Cr experience the same RF inhomogeneity. Other diseases, such as Canavan disease (18–21) and amyotrophic lateral sclerosis (18), are known to produce an increased NAA/Cr ratio with respect to that in control subjects. The methyl group of NAA and other *N*-acetyl compounds have a sharp resonance at 2.0 ppm in the proton spectrum. The exact role of NAA in brain tissue is still unclear; however, most researchers agree that NAA is a specific marker for neuronal damage (NAA is not found is mature glial cells) and may have a role in neuronal metabolism (3, 22). The NAA/Cr ratio is known to decrease in many chronic diseases of the brain, including multiple

sclerosis (23). The increase or decrease in NAA may be related to the metabolic disturbances caused by demyelination versus primary neuronal degeneration. We observed no change in the Cho/Cr ratio in the patients with hearing loss as compared with the volunteers. Cho/Cr is thought to be a marker of abnormal membrane metabolism (24), and the Cho/Cr ratio has been observed to increase in brain tumors (25) and in brain lesions of multiple sclerosis (24).

Effects of Disease Progression

We noted a decrease in the music-stimulated lactate/Cr level among the patients and a decrease in the NAA/Cr level between the first and second visits. Also, all the significant changes during the first visit became insignificant during the second visit as the MR spectroscopic values approached control values. These decreases toward the normal MR spectroscopic levels could indicate biochemical recovery from the initial acute attack.

Central Nervous System Damage versus Peripheral Damage

One of the recurring questions in the study of sudden sensorineural hearing loss is: Where is the damage to the auditory system? Is the damage in the peripheral auditory system or more centrally in the brain? The audiometry tests point toward damage to the cochlea; however, we only measured MR spectroscopic changes in the auditory cortex. Rubel et al (26) have shown neuronal atrophy and degeneration in an auditory brain stem nucleus in which incoming neuronal signals from the cochlear nerve were blocked. These data are consistent with ours in that deafness in one ear causes a decrease of incoming neuronal signals to the auditory cortex, which may be the cause of chronic biochemical changes to NAA.

Summary and Conclusion

Using a single-voxel MR spectroscopic technique, we detected metabolite changes in the auditory cortex of patients with hearing loss that may be useful in monitoring the evolution of disease. Hearing loss patients had a different lactate response to music than did control subjects, and this response changed with time. The patients also had abnormally high NAA/Cr ratios relative to the control group that were independent of sound stimuli. Lactate may be an important indicator of changes in brain activation, and NAA may be an important indicator of chronic damage to the brain in patients with hearing loss.

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References

1. Simons B. Sudden idiopathic sensorineural hearing loss: some observations. *Laryngoscope* 1973;83:1221–1227
2. Behar KL, Den Hollander JA, Stromski ME, et al. High-resolution 1H nuclear magnetic resonance study of cerebral hypoxia in vivo. *Proc Natl Acad Sci* 1983;80:4945–4948
3. Birken DL, Oldendorf WH. *N*-acetyl-L-aspartic acid: a literature review of a compound prominent in 1H-NMR spectroscopic studies of brain. *Neurosci Biobehav Rev* 1989;13:23–31
4. Richards TL, Alvord EC, Peterson J, et al. Experimental allergic encephalomyelitis in non-human primates: MRI and MRS may predict the type of brain damage. *NMR Biomed* 1995;8: 49–58
5. Arus C, Chang Y, Barany M. Proton nuclear magnetic resonance spectra of excised rat brain: assignment of resonances. *Physiol Chem Phys Med NMR* 1985;17:23–33
6. Tunggal B, Hofmann K, Stoffel W. In vivo 13C nuclear magnetic resonance investigations of choline metabolism in rabbit brain. *Magn Reson Med* 1990;13:90–102
7. Pettegrew JW, Kopp SJ, Minshew NJ, et al. 31P nuclear magnetic resonance studies of phosphoglyceride metabolism in developing and degenerating brain: preliminary observations. *J Neuropathol Exp Neurol* 1987;46:419–430
8. Prichard JW. What the clinician can learn from MRS lactate measurements. *NMR Biomed* 1991;4:99–102
9. Sappey MD, Calabrese G, Fein G, Hugg JW, Biggins C, Weiner MW. Effect of photic stimulation on human visual cortex lactate and phosphates using 1H and 31P magnetic resonance spectroscopy. *J Cereb Blood Flow Metab* 1992;12:584–592
10. Hayes C, Tsuruda J, Mathis C. Temporal lobes: surface MR coil phased-array imaging. *Radiology* 1993;189:918–920
11. Singh M. Toward proton MR spectroscopic imaging of stimulated brain function. *IEEE Trans Nuc Sci* 1992;39:1161–1164
12. Tsacopoulos M, Magistretti PJ. Metabolic coupling between glia and neurons. *J Neurosci* 1996;16:877–885
13. Harrer G, Harrer H. Music, emotion and autonomic function. In: Critchley RA, ed. *Music and the Brain*. London, England: William Heinemann Medical Books Limited; 1977:202–232
14. Wallin NL. *Biomusicology: Neurophysiological, Neuropsychological, and Evolutionary Perspectives on the Origin and Purposes of Music*. Stuyvesant, NY: Pendragon Press; 1991:102–107

15. Mazziotta JC, Phelps ME, Carson RE, Kuhl DE. Tomographic mapping of human cerebral metabolism: auditory stimulation. *Neurology* 1982;32:932–937
16. Creutzfeldt O, Ojemann G. Neuronal activity in the human lateral temporal lobe, III: activity changes during music. *Exp Brain Res* 1989;77:490–498
17. Popper K, Eccles J. *The Self and Its Brain*. New York, NY: Springer International; 1977:1–100
18. Miller BL. A review of chemical issues in 1H NMR spectroscopy: *N*-acetyl-L-aspartate, creatine and choline. *NMR Biomed* 1991;4: 47–52
19. Toft PB, Geiss HR, Rolland MO, et al. Magnetic resonance imaging in juvenile Canavan disease. *Eur J Pediatr* 1993;152:750–753
20. Grodd W, Krageloh MI, Klose U, Sauter R. Metabolic and destructive brain disorders in children: findings with localized proton MR spectroscopy. *Radiology* 1991;181:173–181
21. Barker PB, Bryan RN, Kumar AJ, Naidu S. Proton NMR spectroscopy of Canavan's disease. *Neuropediatrics* 1992;23:263–267
22. Gill SS, Small RK, Thomas DGT, et al. Brain metabolites as 1H NMR markers of neuronal and glial disorders. *NMR Biomed* 1989; 2:196–200
23. Richards TL, Bowen JD, Alvord EC, et al. MR brain spectroscopy: basic concepts with emphasis on multiple sclerosis. *Int J Neuroradiol* 1996;2:123–133
24. Richards TL. Proton MR spectroscopy in multiple sclerosis: value in establishing diagnosis, monitoring progression, and evaluating therapy. *AJR Am J Roentgenol* 1991;157:1073–1078
25. Ross B, Michaelis T. Clinical applications of magnetic resonance spectroscopy. *Magn Reson Q* 1994;10:191–247
26. Rubel EW, Hyson RL, Durham D. Afferent regulation of neurons in the brain stem auditory system. *J Neurobiol* 1990;21:169–196

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