An investigation of sensory deficits underlying the aphasia-like behavior of macaques with auditory cortex lesions

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Bilateral auditory cortex lesions in Japanese macaques result in an aphasia-like deficit in which the animals are unable to discriminate two forms of their coo vocalizations. To determine whether this deficit is sensory in nature, two monkeys with bilateral lesions were tested for their ability to discriminate frequency and frequency change. The results indicated that although the animals were able to discriminate between sounds of different frequencies, they were unable to determine whether a sound was changing in frequency. Because the animals' coo vocalizations differ primarily in the predominant direction of their frequency change and not in their absolute frequency content, the aphasia-like deficit of animals with bilateral auditory cortex lesions appears to be a sensory disorder. *NeuroReport* 12:1217–1221 © 2001 Lippincott Williams & Wilkins.

Key words: Animal psychophysics; Aphasia; Auditory cortex disorder; Bilateral lesions; Difference thresholds; Frequency discrimination; Frequency modulation; Macaques; Primates; Vocalizations

INTRODUCTION

The study of cortical lesions in Japanese macaques (*Macaca fuscata*) suggests that these primates possess a cortical mechanism for the perception of their vocalizations similar to that mediating the perception of speech in humans [1,2]. Specifically, unilateral lesions of the left, but not the right superior temporal gyrus result in a transient deficit in their ability to discriminate two forms of their 'coo' vocalizations [3,4], indicating a left hemisphere specialization similar to, but not as strong as, that found in humans. The cortical nature of this deficit is supported by the observation that bilateral lesions result in a complete and permanent inability to discriminate the coos. For these reasons, an understanding of the aphasia-like deficit in Japanese macaques would not only further our understanding of the role of auditory cortex in processing their vocal communications, but could shed light on the sensory aphasia known to follow cortical damage in humans [5,6].

A primary question concerning the aphasia-like deficit is whether it reflects a perceptual deficit, or whether it can be explained in terms of a sensory disorder. Perceptually, the two types of coos used to demonstrate the deficit are produced in different behavioral situations and are thus presumed to have different meanings [7]. One type of coo (referred to as smooth early high or SEH) is a general contact-seeking call, whereas the other type (referred to as smooth late high or SLH) is produced primarily by estrus females seeking male consorts. Thus, the inability to discriminate the coos may reflect a failure to perceive their different meanings just as human aphasia is often described as an inability to perceive the meaning of speech [5,6].

On the other hand, in order to perceive the different meanings of the coos, an animal must first be able to resolve their relevant physical differences. Acoustically, both types of coos are complex tonal signals, ~350 ms in duration, with a fundamental frequency in the region of 625 Hz [8]. Where the two differ is in the temporal position of a frequency inflection that occurs either early (SEH) or late (SLH) within the coo. As a consequence of this difference, the coos can be viewed as tonal signals that either decrease (SEH coo) or increase (SLH coo) in frequency throughout most of their durations (Fig. 1). Indeed, macaques trained to discriminate their coos readily generalize to simple tones that rise or fall in frequency [8]. Accordingly, in order to discriminate the coos, an animal must not only be able to discriminate frequency *per se*, but frequency change as well.

MATERIALS AND METHODS

The goal of this study was to determine whether the coo discrimination deficit that follows bilateral lesions could be explained by a sensory deficit involving the ability to discriminate frequency change. Eight Japanese macaques were used in this study, two of which had received bilateral lesions of auditory cortex [9–11] ~3 years prior to these tests (see Fig. 2). For surgery, an animal was initially anesthetized with ketamine and xylazine and then admin-

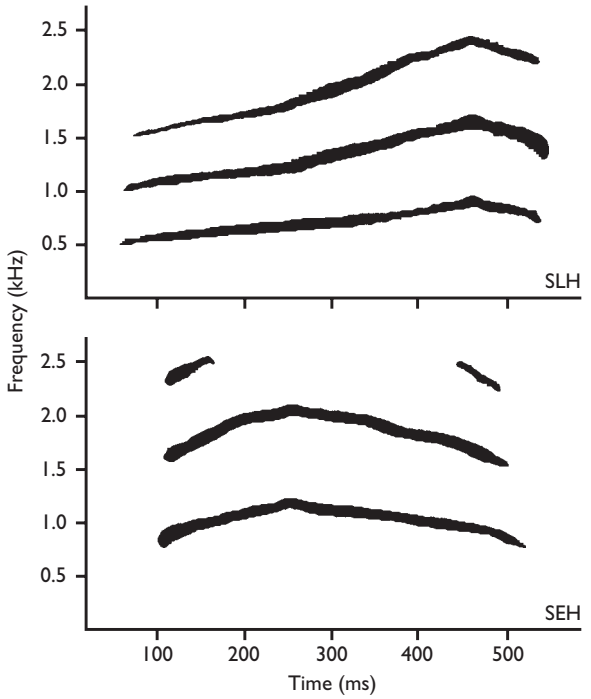

Fig. 1. Sonograms of representative SLH (top) and SEH (bottom) coos. The coos can be characterized as tonal signals that predominantly rise (SLH) or fall (SEH) in frequency.

istered halothane via endotracheal cannula. The lesions, aimed at removing the posterior 3/4 of the superior temporal gyrus, were made under aseptic conditions by subpial aspiration with the aid of a surgical microscope. Following surgery the animal was given acepromazine and butorphanol as necessary to reduce discomfort. For comparison, two normal animals and four animals with unilateral lesions of the superior temporal gyrus were tested. Because the performance of unilateral animals did not differ from that of normal animals when stimuli were presented via a loudspeaker (thus reaching both ears), these animals were combined into a single comparison group. The animals were given a variety of auditory tests, five of which are described here.

Behavioral testing involved the use of a conditioned suppression/avoidance procedure [12]. For the discrimination tests, a thirsty monkey climbed into a primate chair and placed its mouth on a waterspout to receive a slow but steady trickle of water. The animal was first trained to break contact with the spout after the presentation of one type of stimulus by following the sound with a mild electric shock delivered through the water spout. The animal then learned to maintain contact when a different type of sound was presented, as that sound was never followed by shock. Stimuli followed by shock were referred to as warning stimuli, while those not followed by shock were referred to as safe stimuli. Each trial consisted of three presentations of a stimulus from a speaker located 1 m in front of the animal. Following each trial, the response of the animal (i.e. whether or not it broke contact with the spout) was automatically recorded. Breaking contact following a warning stimulus was scored as a hit, while breaking contact following a safe stimulus was scored as a false alarm. To correct for false alarms, an index of performance was derived by the formula: performance = hit rate − (hit rate × false alarm rate) in which scores could range from 1.0 (perfect discrimination) to 0 (failure to discriminate). Hit and false alarm rates were also compared using the binomial distribution to determine if they differed at the 0.01 level of significance. Twenty three percent of trials were warning trials and were randomly interspersed among the safe trials.

Two methods of stimulus presentation were used in this study. In the first, referred to as the method of constant stimuli [13], a measure of overall performance was obtained for a group of stimuli presented in quasi-random order. In the coo discrimination, for example, one of seven possible SEH coos was presented three times during each safe trial, while one of eight possible SLH coos was presented three times during each warning trial. The second method of stimulus presentation, referred to as the method of serial groups [13] was used for the determination of absolute thresholds and difference limens. Stimuli were presented in blocks consisting of 7–10 warning trials and 20–28 safe trials. Within a block of trials the two stimuli to be discriminated remained constant. The acoustic difference between the safe and warning stimuli was reduced between blocks of trials until the animal's performance fell to chance. Testing continued until performance stabilized with thresholds determined by interpolation as the stimulus value yielding a 0.50 level of performance.

Pure tone thresholds were determined in octave steps from 0.063 to 8 kHz using the method of serial groups described above. Testing was conducted in a wire-mesh cage designed to minimize acoustic reflections [14]. The animals were required to break contact with a water spout following the presentation of a tone. Tones were presented at random intervals and were pulsed 6 times per trial (500 ms on, 200 ms off, 30 ms rise–decay). The intensity of a tone was reduced in successive blocks of trials until an animal's performance fell to chance. Thresholds were defined by interpolation as the intensity yielding a 0.50 level of performance.

Following testing, one of the bilateral animals was deeply anesthetized and perfused with 0.9% saline followed by 10% formalin. The brain was removed, photographed, frozen, and sectioned in the coronal plane at 40 μm. One set of sections 1 mm apart was stained (thionine) and used to reconstruct the cortical lesion. The procedures used here were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Toledo, which conforms to standards established by the NIH.

RESULTS

Anatomical results: Cortical reconstructions for one animal with a bilateral auditory cortex lesion are shown in Fig. 2. The lesion removed most of the superior temporal gyrus extending from the insula (medially) to the superior temporal sulcus (laterally). The insular cortex and the rostral pole of the superior temporal gyrus were spared. Based on recent anatomical descriptions of auditory cortex

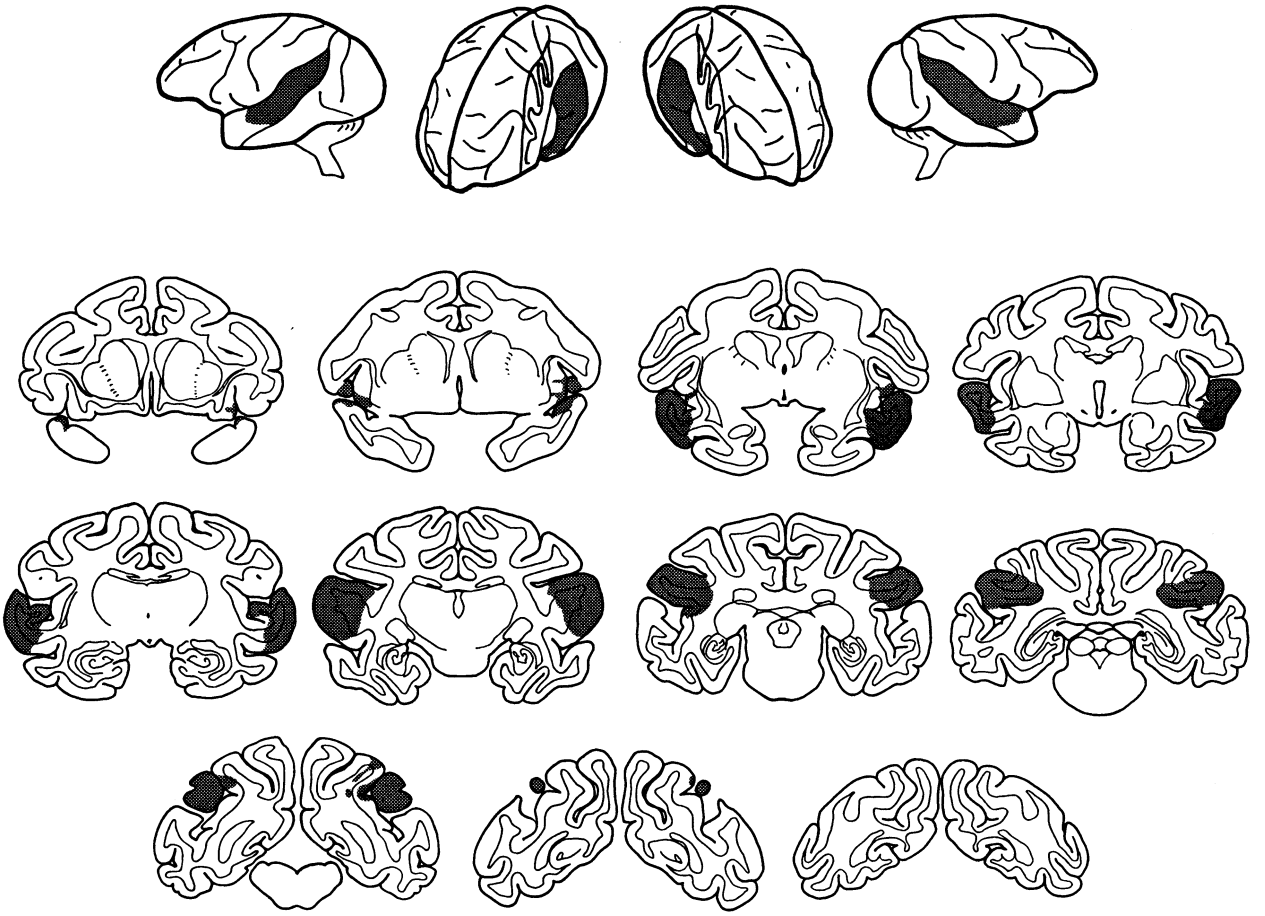

Fig. 2. Cortical reconstructions of one animal with bilateral auditory cortex lesions. The lesions (shading) removed the majority of the superior temporal gyrus bilaterally, including core, belt, and parabelt auditory fields. Sections illustrated were 1.8 mm apart. This animal is represented in Fig. 3 by filled squares.

in this and closely related macaque species [10,11] the lesion included core, belt and parabelt auditory fields. This was substantiated by the severe degeneration and shrinkage throughout the medial geniculate bilaterally [15]. Similar lesions were made in the second bilateral animal and the four unilateral animals, which are currently undergoing additional behavioral tests.

Coo discrimination: The animals were first tested for their ability to discriminate eight SLH coos from seven SEH coos, the same vocalizations previously used to demonstrate the aphasia-like deficit [3,4]. The results indicated that the animals with bilateral lesions were completely unable to discriminate the coos while the comparison animals performed the task easily (Fig. 3a). Because there was no sign of recovery during the 3 years since surgery, it appears that this deficit is permanent.

Pure tone thresholds: Bilateral auditory cortex lesions have been shown to result in elevated absolute thresholds in macaques [15]. Although previous studies have suggested that this hearing loss cannot account for the aphasia-like deficit [16] absolute thresholds were determined for tones at octave steps from 0.063 to 8.0 kHz for the two animals with bilateral lesions and three comparison animals. The results showed that thresholds for the bilateral animals fell within the range of the comparison animals with the minor exceptions of 1 kHz, where one bilateral was 2 dB less sensitive, and 0.5 kHz, where one bilateral was 3 dB more sensitive than the comparison animals. Because this range encompasses the fundamental frequency range of the coos, as well as the stimuli used in the other tests, these results provide additional evidence that the aphasia-like deficit is not the result of a hearing loss.

Frequency discrimination: Frequency difference limens were obtained for discriminating a 625 Hz tone (300 ms in duration) from tones of higher frequency. The 625 Hz stimulus was chosen because it approximated the average fundamental frequency of the coos. Although 300 ms is slightly shorter than the average duration of the 15 vocalizations used in the previous test, it is typical of the duration used for synthetic coos [8,17]. Figure 3b shows that the average frequency difference limen (i.e. the increment in frequency from 625 Hz yielding a 0.50 level of

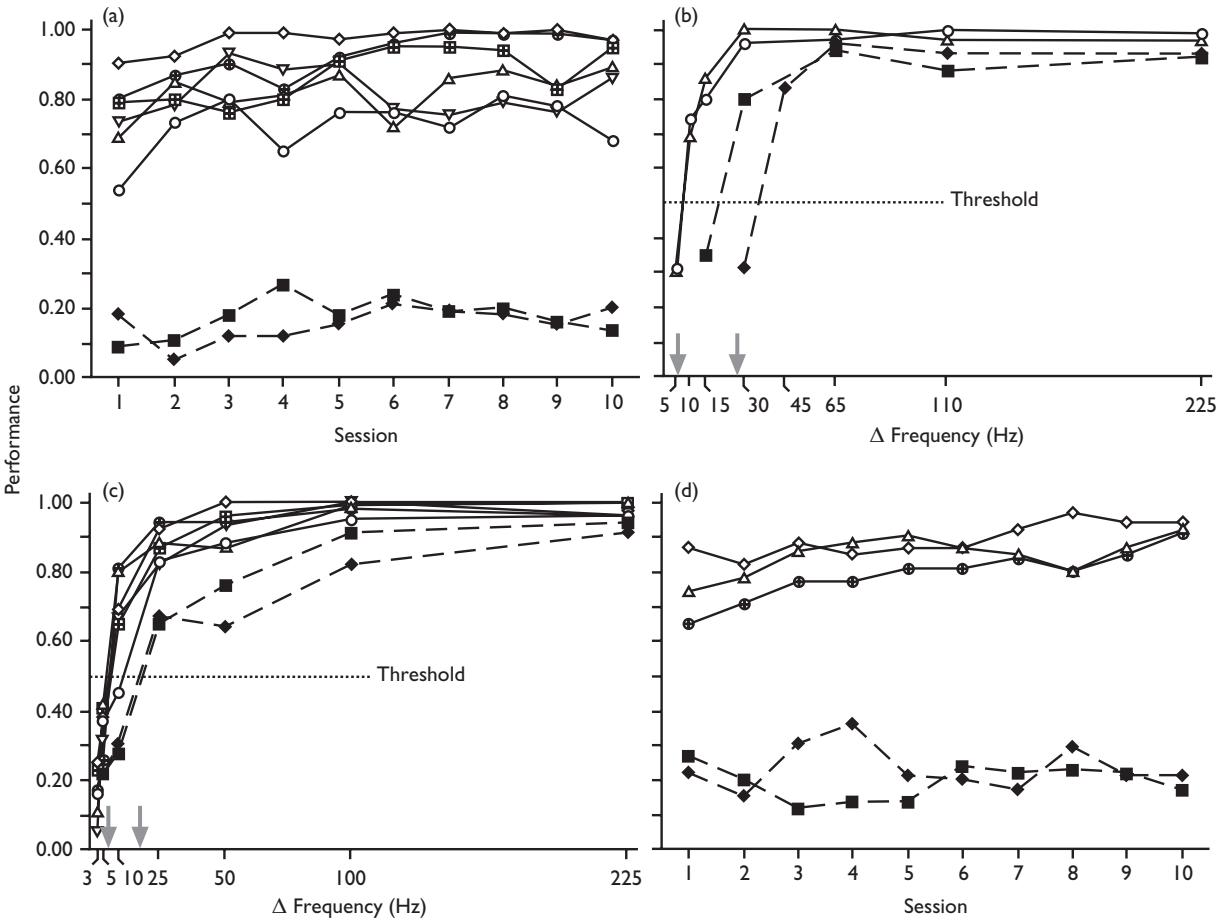

Fig. 3. (**a**) Coo discrimination: behavioral scores of the two animals with bilateral auditory cortex lesions (filled symbols, dashed lines) and six comparison animals (open symbols, solid lines) for the discrimination of eight SLH coos from seven SEH coos. Despite 3 years post-operative recovery, the animals with bilateral lesions remained unable to perform the discrimination. (**b**) Frequency discrimination: psychophysical functions of the two animals with bilateral lesions and two comparison animals for the discrimination of a 625 Hz tone from tones of higher frequency. Although bilateral lesions resulted in a slight elevation of frequency difference limens, this deficit was insufficient to account for the coo discrimination deficit. (**c**) Steady tone versus frequency sweep: psychophysical functions of the two animals with bilateral lesions and six comparison animals for the discrimination of a 625 Hz tone from a descending frequency sweep. Although bilateral lesions resulted in a slight elevation of thresholds, this deficit was also insufficient to account for the coo discrimination deficit. (**d**) Multiple steady tones *vs* frequency sweeps: behavioral scores of the two animals with bilateral auditory cortex lesions and three comparison animals for the discrimination of five descending frequency sweeps from eight steady tones that spanned the same frequency range. With absolute frequency cues rendered ineffective, the bilateral animals were completely unable to perform the discrimination. This deficit accounts for the coo-discrimination deficit.

performance) was 7.5 Hz for the comparison animals and 27.5 Hz for the animals with bilateral lesions. These results indicate a moderate elevation of difference limens after bilateral lesions. However, this change in threshold is not sufficient to account for the inability to distinguish the coo vocalizations because the frequency change in the coos ranged from 50 to 450 Hz, well above the elevated thresholds of the animals with bilateral lesions.

Steady tone** vs **frequency sweep: Because the coos have been characterized as frequency sweeps, thresholds were obtained for discriminating a 625 Hz tone from descending frequency sweeps that began at a higher frequency and ended at 625 Hz. As in a previous test, the stimuli were 300 ms in duration. Figure 3c shows that the average frequency difference limen (i.e. the frequency excursion yielding a 0.50 level of performance) was 7.8 Hz for the comparison animals and 18.5 Hz for the animals with bilateral lesions. Similar thresholds (not illustrated) were found when ascending frequency sweeps (beginning at 625 Hz) and were substituted for the descending frequency sweeps.

Although the results of this test appeared to indicate that the animals with bilateral lesions could discriminate steady tones from tones that were changing in frequency, the test itself was not conclusive. Specifically, it was possible that they were performing the discrimination on the basis of absolute frequency cues (because the warning stimuli contained frequencies not present in the safe stimuli) rather than on the basis of whether the sounds were steady or changing in frequency. The final test was designed to examine that possibility.

Multiple steady tones vs descending frequency sweeps: To eliminate the use of absolute frequency cues, the animals were required to discriminate descending frequency sweeps from a group of steady tones that spanned the same frequency range. The stimuli consisted of eight steady tones (625, 640, 655, 690, 735, 850, 1000 and 1250 Hz) and five descending frequency sweeps (with beginning frequencies of 650, 675, 725, 850 and 1250 Hz and an ending frequency of 625 Hz). As can be seen in Fig. 3d, the animals with bilateral lesions were completely unable to discriminate the frequency sweeps from the steady tones even though all of the sweeps had been easily discriminated from a single 625 Hz tone (see Fig. 3c). In short, although the animals with bilateral lesions could discriminate sounds that differed in absolute frequency, they were unable to determine if a sound was changing in frequency, at least for sounds of the duration and frequencies tested here.

DISCUSSION

The inability of the monkeys with bilateral lesions to determine whether a sound was changing in frequency readily accounts for their inability to discriminate the two types of coos and, indeed, their performance on the two tests was virtually identical (compare Fig. 3a and Fig. 3d). Because the two types of coos overlap in frequency, thereby rendering absolute frequency cues ineffective, and differ only in their predominant direction of frequency change, they could not be discriminated by the animals with bilateral lesions because the animals are unable to determine whether a sound was changing in frequency, much less the direction of the change. Thus, it appears that the inability of the animals with bilateral lesions to discriminate the coos can be explained in terms of a sensory disorder.

These findings are consistent with a growing body of evidence indicating that auditory cortex is necessary for the normal perception of frequency change. In addition to physiological evidence that auditory cortex neurons are selective for frequency change [18–20], bilateral auditory cortex lesions have been shown to disrupt the discrimination of ascending and descending frequency sweeps in both cats and gerbils [21,22]. Similarly, bilateral lesions of the temporal lobe in humans have been shown to result in increased thresholds for detecting a change in a sinusoidally frequency-modulated tone [23]. Our results support these findings and provide evidence that bilateral auditory cortex lesions in primates can result in not just a threshold shift, but in a total inability to determine if a sound is changing in frequency, at least for sounds of the frequencies and durations used here.

CONCLUSION

The inability of Japanese macaques with bilateral auditory cortex lesions to discriminate their coo vocalizations appears to be the consequence of a sensory deficit that is specific to frequency change. Although the animals could discriminate sounds that differed in frequency, they were unable to determine if a sound was changing in frequency. It should be noted that this deficit could only be demonstrated when the animals were prevented from using absolute frequency differences to perform the task. Because this deficit readily accounts for the inability of Japanese macaques to discriminate their coo vocalizations, the question arises as to the degree to which a similar deficit could account for the various language disturbances that follow temporal lobe damage in humans.

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