



Lateralization of Phonetic and Pitch Discrimination in Speech Processing

Robert J. Zatorre, Alan C. Evans, Ernst Meyer, Albert Gjedde

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kilogram of body weight, injected intramuscularly). Squirrel monkeys received 2 mg of MPTP per kilogram of body weight, whereas cynomolgus monkeys received a mean of 0.35 mg of MPTP per kilogram of body weight.

15. The MPTP was administered every third day until animals were akinetic, unresponsive to stimuli, unable to climb, and not eating effectively on their own. A rating score (for any given pair of animals) of at least 30 (10) needed to be achieved on three consecutive days before cessation of MPTP injections and random assignment to treatment groups. Administration of MPTP and degree of initial symptomatology were similar for animals chosen to receive saline or G_{M1} ganglioside treatment.
16. During the first several weeks of the study, all animals required intensive hand feeding and hydration and sometimes received dopamine agonist intramuscularly (LY-171555; 0.1 mg per kilogram of body weight) to facilitate feeding.

Animals were fed fruit, crushed chow, liquid diet (Primate Liquid Diet, BioServ, Frenchtown, NJ), and Gatorade. Occasionally, feedings needed to be supplemented with parenteral lactated Ringers solution (15 ml twice daily). Four to 5 weeks after MPTP was stopped, G_{M1}-treated monkeys resumed spontaneous eating and drinking while many of the saline-treated monkeys needed to be continued on some type of nutritional support for the 6 to 8 weeks of study. Animal care was administered in accordance with institutional guidelines.

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Lateralization of Phonetic and Pitch Discrimination in Speech Processing

Robert J. Zatorre,* Alan C. Evans, Ernst Meyer, Albert Gjedde

Cerebral activation was measured with positron emission tomography in ten human volunteers. The primary auditory cortex showed increased activity in response to noise bursts, whereas acoustically matched speech syllables activated secondary auditory cortices bilaterally. Instructions to make judgments about different attributes of the same speech signal resulted in activation of specific lateralized neural systems. Discrimination of phonetic structure led to increased activity in part of Broca's area of the left hemisphere, suggesting a role for articulatory recoding in phonetic perception. Processing changes in pitch produced activation of the right prefrontal cortex, consistent with the importance of right-hemisphere mechanisms in pitch perception.

Extracting information from complex signals is one important function of the auditory nervous system. The cortex is crucial for many aspects of auditory cognition (1), although considerable subcortical neural processing occurs before information reaches the cortex. There is much evidence that specialized speech-decoding mechanisms rely on perisylvian areas in the left cerebral hemisphere (2), whereas certain aspects of pitch perception depend more on systems within the right hemisphere (3). Positron emission tomography (PET) studies have demonstrated activation of the primary auditory cortex with simple auditory stimuli (4) and bilateral activation of the superior temporal gyrus during passive word presentation (5, 6), but the precise neural substrate for specialized linguistic and nonlinguistic processing mechanisms remains largely unknown.

We measured cerebral blood flow (CBF) changes with PET to examine several issues. First, we wished to clarify the role of primary versus secondary auditory regions

in speech perception. We hypothesized that simple auditory stimulation should lead to activation of the primary cortex, whereas more complex signals should lead to activity in associative areas. Second, we tested the hypothesis that phonological processing depends on the left temporoparietal cortex

(5) by using a phonetic discrimination task. Third, we attempted to dissociate linguistic from nonlinguistic processing by requiring judgments of pitch changes in the speech syllable, which we hypothesized to involve right-hemisphere mechanisms (3).

Ten adult volunteers (7) were given PET scans with the paired-image subtraction paradigm (5, 8, 9). Two types of stimuli were used: pairs of noise bursts (10) and pairs of consonant-vowel-consonant real speech syllables. The vowels in any given syllable pair were always different, but the final consonant differed in half of the pairs (Table 1); in addition, the second syllable had a higher fundamental frequency in half of the pairs and a lower frequency in the other half (11).

The study included five conditions (Table 1) arranged in a subtractive hierarchy (5). The first was a silent baseline; in the noise condition, subjects pressed a key to alternate pairs of noise bursts; in the passive speech condition, subjects listened to the syllables and pressed a key to alternate stim-

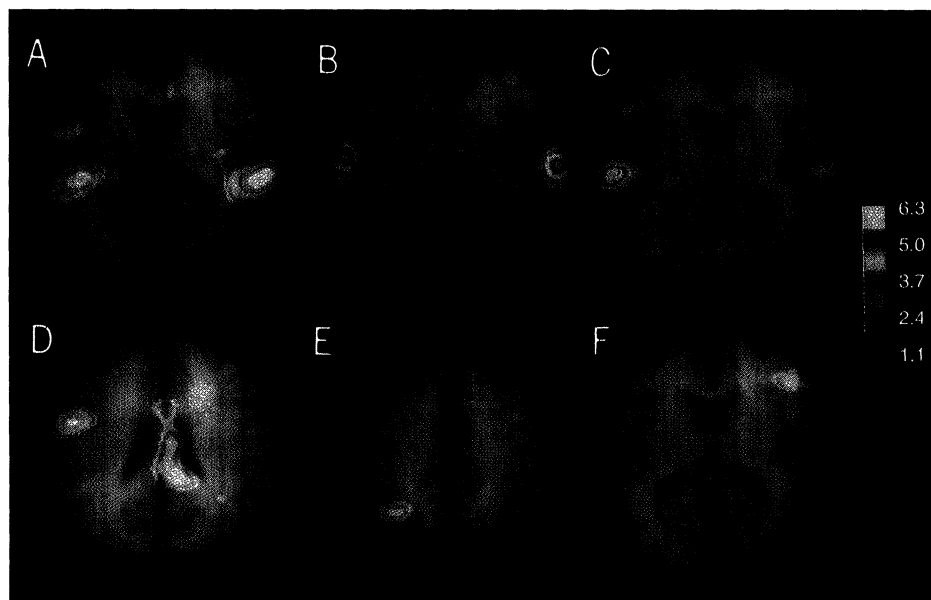
Table 1. Summary of paradigm. The five conditions are arranged hierarchically (5) so that subtractions may be performed holding constant all but the variables of interest. The last three conditions involved identical stimulation, but the expected response [key press (Y) or no response (N)] varied according to the instructions; the number of key presses expected was equal for all conditions. Accuracy and reaction time data, gathered on-line during scanning, substantiate that subjects were performing the intended judgments.

Condition	Stimulus	Response	Example	Mean percent correct	Mean reaction time (ms)
Baseline	Silence	None			
Noise	Noise bursts	Alternating key press			
Passive speech	Speech syllables	Alternating key press	fat-tid (Y) tig-lat (N) bag-big (Y) fat-tid (N) tig-lat (N) bag-big (Y)	97.9	1382
Phonetic	Speech syllables	Key press to same final consonant	fat-tid (N) tig-lat (N) bag-big (Y)		1576
Pitch	Speech syllables	Key press to rising pitch	fat-tid (N) tig-lat (Y) bag-big (N)	88.5	1663

McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada H3A 2B4.

*To whom correspondence should be addressed.

Fig. 1. Averaged PET subtraction images superimposed upon averaged MRI horizontal slices, showing significant focal CBF increases in each condition. Accuracy in matching functional and anatomical data across subjects is indicated by the extent to which individual sulci may be distinguished in the averaged magnetic resonance image. The range of *t* values for the PET data (Table 2) is coded by the color scale. **(A)** Noise – Baseline condition (*z* = +10 mm); significant foci were observed bilaterally within Heschl's gyri with noise stimulation. **(B and C)** Speech – Noise condition (*z* = –5 and +8 mm, respectively); bilateral activation was seen (i) in the superior temporal gyrus (B), anterior to Heschl's gyri, while subjects listened passively to speech, (ii) in the left inferior frontal cortex (B and C), and (iii) in the left posterior temporal area (C). [The posterior midline focus visible in (C) was below the threshold for significance.] **(D and E)** Phonetic – Speech condition (*z* = +24 and +45 mm, respectively); comparison of phonetic judgment to passive speech revealed CBF increases in the superior portion of Broca's area (D) and within the left superior parietal lobe (E). A portion of the activation of the cingulate gyrus obtained in this subtraction is also visible (D). **(F)** Pitch – Speech condition (*z* = +9);



judging pitch changes of the same syllables, as compared to passive listening, produced significant activity in the right prefrontal cortex.

Table 2. Significant activation foci for the four subtraction conditions (9). We report only positive activation peaks located within the parenchyma that exceed a statistical criterion of *P* < 0.04 (two-tailed), corresponding to a *Z* score of 2.06 or greater. Stereotaxic coordinates refer to medial-lateral position (*x*) relative to midline (positive = right), anterior-posterior position (*y*) relative to the anterior commissure (positive = anterior), and superior-inferior position (*z*) relative to the commissural line (positive = superior). Designation of Brodmann areas is approximate.

Coordinates (mm)			<i>t</i> Value	<i>Z</i> Score	Area	Brodmann number
<i>x</i>	<i>y</i>	<i>z</i>				
<i>Noise – Baseline</i>						
–40	–23	49	5.64	3.59	Left pre/post central gyrus	3/4
–43	6	–5	5.02	3.22	Left superior temporal gyrus (anterior)	22
55	–30	8	4.88	3.14	Right superior temporal gyrus (posterior)	42
–46	–30	13	4.73	3.05	Left transverse temporal gyrus (Heschl)	41
–7	8	42	4.73	3.05	Midline cingulate gyrus (anterior)	32
15	–57	–15	4.56	2.94	Right lateral cerebellum	
12	6	57	3.71	2.43	Right supplementary motor area	6
–4	–2	63	3.27	2.17	Midline supplementary motor area	6
<i>Speech – Noise</i>						
60	–14	0	5.87	4.25	Right superior temporal gyrus (anterior)	21/22
–58	–21	8	5.60	4.06	Left superior temporal gyrus (posterior)	22/42
–58	–4	–5	5.05	3.67	Left middle temporal gyrus	21
54	18	–12	3.78	2.76	Right superior temporal gyrus (anterior)	38
–54	24	–5	3.60	2.63	Left inferior frontal gyrus	47
–50	22	11	2.82	2.07	Left inferior frontal gyrus	45
<i>Phonetic – Speech</i>						
–48	3	24	3.95	3.09	Left Broca's area (posterior)	44/6
7	–31	21	3.25	2.56	Midline cingulate gyrus (posterior)	31
15	–93	–11	2.84	2.25	Right occipital pole	17
–29	–59	45	2.71	2.16	Left superior parietal lobe	7/40
–1	13	27	2.66	2.11	Midline cingulate gyrus (anterior)	24
–62	–35	–18	2.62	2.08	Left inferior temporal gyrus	20
<i>Pitch – Speech</i>						
46	32	9	2.73	2.24	Right inferior frontal gyrus	45/46
34	8	30	2.65	2.18	Right middle frontal gyrus	9
–24	1	33	2.53	2.08	Left supplementary motor area	6
4	–83	–11	2.50	2.06	Midline occipital lobe	18

ulus pairs; in the phonetic condition, subjects listened to the same speech stimuli but responded when the stimuli ended with the same consonant sound; in the pitch condition, subjects listened to the same syllables but responded only when the second item had a higher pitch than the first (12).

When the results from the baseline condition were subtracted from the noise condition, activation was observed bilaterally approximately within the transverse gyri of Heschl (Fig. 1A and Table 2), corresponding to the primary auditory cortex (13), as predicted. Additional significant peaks in the left motor-sensory hand area and the right lateral cerebellum are likely related to the motor demands associated with right-hand key pressing.

Subtraction of the noise condition from the passive speech activation pattern yielded several foci along the superior temporal gyrus in both hemispheres (Fig. 1B). This region contains several cytoarchitecturally distinct cortical fields responsive to auditory stimulation that receive input both from the medial geniculate nucleus and from corticocortical connections (14). It is therefore likely to be

involved in higher order auditory processing of complex signals. One left-lateralized focus in the posterior superior temporal gyrus (Fig. 1C) was also identified. Significant peaks were also observed in the left inferior frontal lobe in this subtraction (Fig. 1B and Table 2); similar findings have previously been interpreted as relating to semantic processing (15).

In the subtraction of passive speech from the phonetic condition, activity was largely confined to the left hemisphere: the largest increase was observed in part of Broca's area near the junction with the premotor cortex (Fig. 1D) and in a superior parietal area (Fig. 1E). There was also activation (Table 2) in the cingulate gyrus (16), the right

occipital pole (17), and the left inferior temporal gyrus (18). The prediction that pitch processing would involve right-hemispheric mechanisms was confirmed in the pitch condition minus passive speech subtraction, with two foci observed in the right prefrontal cortex (Fig. 1F and Table 2). In these latter two subtractions both stimuli and responses were identical; only the nature of the cognitive processing required changed, as a function of the instructions. The dissociable patterns of activity observed must therefore reflect the fundamentally different nature of the neural mechanisms involved in analysis of phonetic and pitch information.

Our results, taken together, support a model whereby auditory information undergoes discrete processing stages, each of which depends on separate neural subsystems. The functional characteristics of the primary auditory regions can be dissociated from those of more anterior cortical areas in the superior temporal gyrus, which were activated bilaterally by the speech stimuli but not by noise, with the exception of one site in the left temporal pole. Moreover, speech produced no further activation in the primary region beyond that observed with noise bursts with similar acoustic properties. These findings imply that the primary cortex contributes to early acoustic analysis of all incoming signals, whereas associative areas are responsible for higher order signal processing (14). There was no additional activity in the temporal cortices in either the phonetic or pitch conditions relative to passive speech, suggesting that complete perceptual analysis—both linguistic and nonlinguistic—takes place in the temporal lobe; however, the nature of the judgment to be made makes demands on neural systems different from those involved in perceptual analysis.

Specifically, when a phonetic decision is required, there is a large focus in part of Broca's area in the left hemisphere. Damage to Broca's area has long been associated with nonfluent aphasia and articulatory disorders (2, 19), but lesions in and adjacent to this zone can also give rise to phonetic perceptual disturbances (20). We propose that in making the phonetic judgment, subjects must access an articulatory representation involving neural circuits that include Broca's area. The left posterior temporal region activated with passive speech (Fig. 1C) may represent the initial stage of phonetic analysis (5), but in order to determine that the [g] in "bag" and "pig" is the same phonetic segment, the auditory features of the stimulus, extracted by temporal-lobe mechanisms, must be related to articulation (21). This hypothesis is consistent with the motor theory of speech perception (22), which proposes that phonetic

decoding depends on access to information about the articulatory gestures associated with a given speech sound. Access to a motor code may not necessarily be required for semantic processing, however, because no Broca's area activation was observed with passive speech, but subjects were still likely processing meaning (23).

The left parietal area also identified in the phonetic condition is near the superior aspect of the supramarginal gyrus, which has been implicated in phonological processing in neuropsychological studies (24). It is consistent with our data to suggest that phonological processing is accomplished through a network including the left posterior temporal and parietal regions as well as Broca's area, although each region's precise contribution remains to be elucidated.

As predicted, right-hemispheric mechanisms appear to be crucial in making judgments related to pitch (3). The right prefrontal cortex may contribute to many distinct functions (25), but in this experiment its activation was specific to the pitch condition. We speculate that it may form part of a distributed network involved in maintenance of pitch information in auditory working memory, an idea supported by anatomical data (26) and by the finding that focal lesions to either the right superior temporal gyrus or to the right frontal lobe result in deficits in retention of pitch (27).

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(MRI) studies (63 slices, 2 mm thick) were obtained and co-registered with the PET data [A. C. Evans, S. Marrett, J. Torrescorzo, S. Ku, L. Collins, *J. Cereb. Blood Flow Metab.* **11**, A69 (1991)]. An orthogonal coordinate frame was then established based on the anterior-posterior commissure line as identified in the MRI volume [A. C. Evans *et al.*, *NeuroImage*, in press], which allowed resampling of MRI and PET data sets into a standardized stereotaxic coordinate system [J. Talarach and P. Tournoux, *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme, New York, 1988)]. The PET images were reconstructed with a 20-mm Hanning filter to overcome residual anatomical variability, normalized for global CBF value, and averaged across subjects for each activation state; the image volume of the mean state-dependent change was obtained (8). Because no significant variation in image variance was detected, the volume was converted to a *t*-statistic volume by dividing each voxel by the mean SD in normalized CBF for all intracerebral voxels (K. J. Worsley, A. C. Evans, S. Marrett, P. Neelin, *J. Cereb. Blood Flow Metab.*, in press). Anatomical and functional images were merged to allow direct localization on the magnetic resonance images of the activation peaks. The distribution of peaks was then searched for significant changes with change-distribution analysis (5, 8).

10. Noise bursts were prepared by segmenting and filtering white noise to approximate the acoustic characteristics (amplitude, duration, onset-offset shape, and spectral shape) of the speech. All stimuli were presented binaurally with insert earphones at an average sound pressure level of 75 dB.
11. Forty pairs of syllables (half words, half nonwords) were used (see Table 1). Pitch change and phonetic differences were uncorrelated across stimuli. Two tokens of each syllable were recorded to avoid extraneous acoustic cues. Mean interstimulus interval was 300 ms; intertrial interval depended on reaction time but had a maximum of 3 s and a minimum of 1 s. Scans were performed with eyes open but in dimmed room illumination.
12. A different random order of stimuli was presented during each condition. Subjects were given instructions regarding each task only immediately before the scan but were allowed several practice trials. The order of the first three conditions (Table 1) was fixed for all subjects, but the order of the pitch and phonetic conditions was counterbalanced across subjects.
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17. We speculate that occipital activation may be due to extraneous visual stimulation produced by eye movements.
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TECHNICAL COMMENTS

Neocortex Development and the Cell Cycle

S. K. McConnell and C. E. Kaznowski report (1) that environmental factors can determine the laminar fate of ferret neocortical neurons during the last mitotic division of their ventricular zone precursors. They suggest that the decision of a cortical ventricular zone precursor to generate a deep-layer neuron is made in late S-phase near the transition into G₂ of the cell cycle. There is an alternative explanation for the data that is consistent with other findings that suggest a laminar fating of earlier ventricular zone precursors to the neocortex.

McConnell and Kaznowski find that, among migrating neurons, 90% of E29 cells labeled with [³H]thymidine and transplanted 2 hours later into the neonatal host ventricular zone migrate to the superficial (2/3) neocortical layers. However, 90% of these cells transplanted 6 hours later (removed after 4 hours and transplanted 2 hours after that) migrate to the deep (5/6/subplate) layers. Thus, within a 4-hour period near the end of S-phase, 90% of cortical cells must change their laminar fate. If these cells have an S-phase of 8 hours and an unsynchronized cell cycle as stated in (1), then only the 25% of the cells that are in the first 2 hours of S-phase and transplanted 2 hours after labeling [rather than the observed 90% in (1), figure 2A] should have escaped the deep-layer decision phase in the last 4 hours of S-phase. If the

deep-layer decision phase of the cell cycle happened later in S-phase or in G₂, then fewer cells transplanted at 6 hours after labeling should have reached the decision phase before transplantation.

Only 20% or less of the transplanted E29 cells actually migrate out of the host ventricular zone into the host neocortical lamina [as detailed by McConnell (2)]. It is possible that one of the dissociation, culturing, or transplantation procedures used in (1) selected for different 20% subpopulations to migrate among the cells transplanted 2 hours, rather than 6 hours, after labeling. This explanation implies that there were heterogeneous ventricular zone populations among which to select. Heterogeneous ventricular zone populations have been revealed by combining retroviral lineage tracing and [³H]thymidine autoradiography (3). In addition, data about cortical genotype ratios in mice produced from blastocyst chimeras have suggested that separate precursor populations may give rise to deep and superficial layer cortical neurons (4). We have recently found (5) through retroviral lineage tracing of the progeny of individual ventricular zone cells that many mammalian neocortical neuronal clones are restricted to deep, rather than superficial, layers. However, these studies (3–5) test for fating or specification of cells, but not if the cells are irreversibly committed to a phenotype; nor do they test whether the commit-

ment can be overcome by environmental cues.

McConnell and Kaznowski also find that most cells lightly labeled with [³H]thymidine (that have presumably divided more than once in the host tissue) migrate to superficial cortical lamina. Once again, these cells may represent a selected subpopulation that is already fated to produce superficial cortical neurons. One would expect continued division by these cells, although the postnatal host tissue environment may artificially limit the total number of divisions by these precursors.

Derek van der Kooy
Neurobiology Research Group,
Department of Anatomy,
University of Toronto,
Toronto, Canada M5S 1A8

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Response: Our experimental design specifically addressed the possibility that the ventricular zone might contain a heterogeneous mixture of precursor cells [reference 20 in (1); (2)]. Van der Kooy posits that different subpopulations of precommitted cells migrate selectively when transplanted at different times in the cycle. In other words, the postmitotic daughters of committed upper-layer precursors migrate if and only if they are transplanted in S-phase (at 0 hours), and the daughters of committed deep-layer precursors do not migrate when transplanted in S-phase. At later times (4 to 24 hours) the situation would have to reverse: the postmitotic daughters of committed upper-layer precursors never migrate when cells are removed at or after 4 hours after labeling, whereas the postmitotic daughters of committed deep-layer precursors only migrate when removed at or after 4 hours. Such a complex set of rules and behaviors seems a far less likely explanation than a simple change in fate of a single population of cells. However, the possibility of differential selection or survival of precommitted cells is an important problem to address in any transplantation study, so we performed an additional analysis of our data.

Our hypothesis—that S-phase environment determines cell fate—generates an easily examined prediction. If cells are sensitive to environmental determinants in