4-base recognition sequence) (Fig. 2). These were features of the fragile X CGG repeat amplification.

We propose several hypotheses that might explain the variability of symptoms in heterozygotes: (i) an effect of the amount of gene product, such as occurs with the low density lipoprotein receptor defect in type II hypercholesterolemia (*22*); (ii) differential parental inheritance of mutations, such as in Angelman and Prader-Willi syndromes (*23*); or (iii) a disturbance of a signal transduction pathway in which myotonin–protein kinase is only one of the disease-producing factors. Each of these hypotheses can be directly examined given our new molecular knowledge of myotonin–protein kinase.

These studies provide a simple method for identification of unstable genetic elements in the human genome. Although we used oligonucleotides as probes and nuclear DNA clones as targets, it is logical to search for other unstable genes by screening cDNA libraries for GC-rich triplet repeats. The lessons of fragile X syndrome, Kennedy disease, and now DM are consistent. Heritable disorders that exhibit the feature of anticipation or molecular imprinting (*24, 25*) would appear worthy of investigation as reported here for DM. Furthermore, since somatic genetic instability is demonstrated for the CGG repeat in the fragile X syndrome, genes containing unstable repeats may be involved in neoplasia and possibly aging, in which somatic mutations are implicated in disease.

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16. Genomic DNAs (100 ng) were mixed with 3 pmol of each primer in a total volume of 15 μl containing 10 mM tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 200 μM of each of the 4 dNTPs, 4 μCi of α-[^{32}P]dCTP, and 0.75 units of AmpliTaq DNA polymerase. The reactions were heated to 95°C for 10 min and followed by 25 cycles of denaturation (95°C, 1 min), DNA reannealing (54°C, 1 min), and elongation (72°C, 2 min). The radioactive PCR products were combined with 95% formamide loading dye and then heated to 95°C for 2 min before electrophoresis through a 6% denaturing DNA sequencing gel. Allele sizes were determined by migration relative to an M13 sequencing ladder. For analysis by 3% agarose gel electrophoresis, 200 ng of genomic DNA were amplified in a final volume of 100 μl using the same buffer, 250 μM of the 4 dNTPs and 0.5 unit of AmpliTaq DNA polymerase. The reactions were heated to 95°C for 5 min and then subjected to 32 cycles of 94°C for 1 min 57°C for 1 min, and 72°C for 3 min.
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The Linguistic Basis of Left Hemisphere Specialization

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In humans the two cerebral hemispheres of the brain are functionally specialized with the left hemisphere predominantly mediating language skills. The basis of this lateralization has been proposed to be differential localization of the linguistic, the motoric, or the symbolic properties of language. To distinguish among these possibilities, lateralization of spoken language, signed language, and nonlinguistic gesture have been compared in deaf and hearing individuals. This analysis, plus additional clinical findings, support a linguistic basis of left hemisphere specialization.

THE LEFT HEMISPHERE OF THE HUMAN brain is specialized for language. The underlying basis of this specialization has been controversial, and it has not been clear if this brain system is uniquely designed for language processing or if it derives from a more general specialization based on motor control (*1*) or symbolization (*2*). Until recently most of our knowledge regarding hemispheric specialization for language has come from the study of spoken languages. In contrast, we have now addressed these competing hypotheses by studying native users of American Sign Language (ASL) (*3, 4*).

ASL is a natural language with structural properties akin to those of spoken languages (*5–10*). After left hemisphere injury deaf signers exhibit sign language aphasia, and right hemisphere damage can result in severe visuospatial disruption but leaves signing intact (*3*). Thus, despite auditory deprivation, deaf users of a signed language show a complementary hemispheric specialization like that of spoken language users. Some researchers have used this evidence to suggest that the left hemisphere is uniquely predisposed for mediation of language, both spoken and signed (*11*). Others argue that left hemisphere specialization for signed and spoken language derives from the left hemisphere's more general role in controlling changes in the position of oral and manual articulators (*12*). Under this interpretation, any skilled motoric movement, such as the execution

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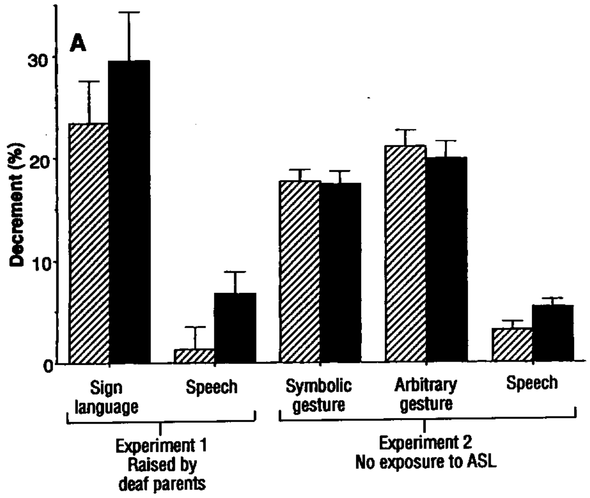
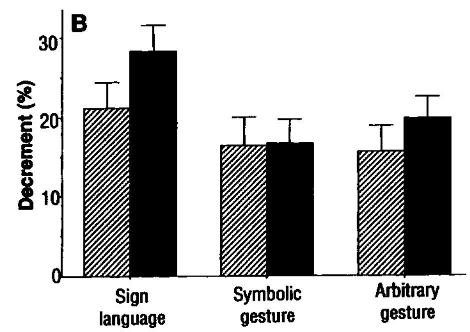
Fig. 1. (**A**) Performance of hearing subjects for sign language, speech, and gesture. Left hemisphere specialization for sign and speech is indicated, whereas no asymmetry for arbitrary or symbolic gesture is indicated. Experiment 1, 16 ASL-English bilinguals (8 males, 8 females); mean age, 35. Subjects were born to deaf parents and raised in signing households. Experiment 2, 48 hearing subjects (24 males, 24 females); mean age, 22. Subjects had no exposure to ASL. (**B**) Differential specialization for sign language is indicated, versus no asymmetry for symbolic and arbitrary subjects. Deaf signing subjects $n = 12$ (6 males, 6 females); mean age, 33. All deaf subjects born to deaf parents and raised in signing households. Confidence bars, SEM; solid bars, right hand; striped bars, left hand.





of nonlinguistic conventionalized gestures (for example, waving good-bye), falls under left hemisphere control. A third group suggests that the expression and comprehension of symbols underlies left hemisphere specialization of linguistic systems (*2*). The study of hemispheric specialization for sign language and nonlinguistic gesture in deaf signers allows resolution of these competing hypotheses because gesture and linguistic symbol are transmitted in the same modality. We therefore examined patterns of hemispheric specialization for sign language, gesture, and speech in deaf and hearing populations to determine the underlying basis of the left hemisphere specialization for language.

We have chosen the concurrent activities paradigm (*13*) for inferring hemisphere differences in the production of speech, sign language, arbitrary gestures, and symbolic (conventionalized) gestures. This procedure assesses the amount of interference produced in a dual-task situation. The relative degree of disruption (as measured, for example, by percent decrement in the rate of finger tapping) when the right, as compared to the left, hand is performing the concurrent task provides the basis for inferring relative involvement of the left and right hemisphere. The interference patterns have been interpreted as an index of intrahemispheric resource competition, following the functional cerebral distance principle, which states that the degree to which two simultaneous activities affect each other varies inversely with the functional distance between the cerebral region in which the respective processes are represented (*14*).

An examination of the relative pattern of tapping disruption under concurrent conditions of shadowing (copying) speech, sign language, arbitrary motoric gesture, and symbolic gesture allows inferences about the relative degrees of lateralization of these various activities and, thereby, should provide insights into the determinants of left hemisphere specialization. Specifically, to the extent that lateralization of language derives from the special characteristics of linguistic systems, we expect speech and sign to produce similar patterns of right-hand (left hemisphere) interference in fluent users. In contrast, to the extent that motoric factors underlie the determination of lateralization, we expect sign language and nonlinguistic manual gestures to show similar patterns of interference as they share common manual articulators, while spoken language would be expected to show a different pattern of interference due to differences in articulator control. Finally, if the degree of symbolization is a determinant of lateralization, we may expect speech, sign language, and symbolic gesture to show similar patterns of interference, whereas interference patterns for arbitrary nonmeaningful gestures would differ because of the lack of symbolic content in this class of gestures.

We have performed three experiments using the concurrent activities procedure with hearing and deaf adults with no brain damage. Our first experiment sought to determine whether sign language would show a similar pattern of left hemisphere specialization as that expected for spoken language in native users of ASL and English. Subjects consisted of 16 right-handed, hearing, native signers, all of whom were offspring of deaf parents and raised in a signing environment. All of these subjects were employed as certified interpreters for the deaf.

The subjects' task was to shadow (repeat) a list of common, one-handed ASL signs and English words presented on videotape and audiotape, respectively. The stimuli were presented at a rate of one word or sign per second. While shadowing these stimuli, subjects were to concurrently tap, as quickly as possible, a telegraph key connected to a microcomputer, which recorded the number of taps in each 30-s trial. The order of the stimuli lists (ASL or English) was counterbalanced among subjects and so was the initial hand used to tap. Baseline tapping rates for each hand were collected before and after the concurrent task exercises and were averaged. A percent decrement score was computed for each hand (baseline − concurrent rate/baseline rate × 100) with the averaged baseline score (*15*).

Percent decrement scores for the first experiment are shown in Fig. 1A. There is a statistically significant (*16*) difference between the results for the ASL stimuli relative to speech stimuli (mean ± SE = 26.5 ± 4.4% for ASL versus 4.1 ± 2.2% for speech). The difference between the results for right and left hands was also significant (18.2 ± 3.4% for right and 12.4 ± 3.1% for left), and the differences were nearly identical for the two types of stimuli. Both speech and sign produced significantly greater right-hand than left-hand tapping disruption, suggesting greater overall left hemisphere involvement for both of these linguistic activities despite the obvious differences attributable to language modality.

Our second experiment was designed to address whether greater left hemisphere involvement also reflects skilled motoric or general symbolic performance. We sought to determine the relative patterns of lateralization for speech, arbitrary gestures, and symbolic gestures. To this end, we tested 48 right-handed, hearing users of English with no knowledge of any sign language on a concurrent activities procedure involving the shadowing of speech and manual gestures.

The shadowing stimuli consisted of common English words and two types of manual gestures presented on either audiotape or videotape at a rate of one item per second. The gestures included symbolic gestures, such as waving good-bye or giving the thumbs-up, as well as arbitrary gestures that comprised nonmeaningful sequences of limb movement adapted from the Kimura and Archibald Movement Copying Test (*17*). The gestures were formationally complex, requiring both fine hand movement and proximal limb movements and were similar to those found in sign language. The procedure and apparatus were the same as in the previous experiment.

The percent decrement scores were different for the symbolic gestures and arbitrary gestures stimuli relative to those for speech stimuli (17.4 ± 1.25%, 20.5 ± 1.65%, and 4.2 ± 0.8%, respectively). The left-right differences for speech stimuli were consistent with that found in experiment 1 (5.5% in experiment 1 versus 2.3% in experiment 2). The left-right differences for the two gesture-type stimuli were not significantly different from zero.

Thus, there were significant differences between shadowing of speech and symbolic and arbitrary manual gestures, with only the speech condition showing an asymmetry in the direction of greater right-hand disruption. These findings replicate those found for the speech condition of experiment 1. No statistically significant hand asymmetries were found for either arbitrary or symbolic gestures; this result is in contrast to the greater right-hand interference for sign shadowing in experiment 1. Taken together, the results of the first two experiments suggest that the greater right-hand interference for sign language shadowing is not attributable to skilled motor movement nor is it a function of symbolization but instead derives from the linguistic nature of the movement.

Our third experiment addressed the question of whether a dissociation would be observed in lateralization patterns for sign (that is, linguistic) and nonlinguistic gesture in deaf native signers. To examine the relative pattern of lateralization for linguistic and nonlinguistic hand movements, we examined performance of 12 right-handed, congenitally deaf, native signers, born of deaf signing parents. All subjects reported ASL as their preferred mode of communication.

The apparatus, procedure, and stimuli lists were the same as those used in the previous experiments. Stimuli consisted of a list of common ASL signs, a list of symbolic gestures, and a list of arbitrary gestures, presented on videotape at the rate of one item per second. The arbitrary gestures and signs were matched closely for complexity. Subjects were to shadow the stimuli while tapping a response key with either their right or left index finger.

Percent decrement in tapping scores for this experiment are shown in Fig. 1B. There is a significantly greater right-hand interference for signing (28.3 ± 3.2% versus 21.0 ± 3.3% for right versus left hand, respectively), but nearly equal amounts of interference were found for symbolic gestures (right hand = 16.6 ± 3.0% versus 16.4 ± 3.6% for left hand) and for arbitrary gestures (*18*) (19.8 ± 2.7% versus 15.6 ± 3.3% for right versus left hand).

For deaf subjects, only shadowing of sign language resulted in significantly greater right-hand interference. No significant asymmetries were found for the shadowing of either arbitrary or symbolic gestures. This result provides additional evidence that sign language production is subserved by the left hemisphere, even in deaf subjects. The difference in interference patterns between the signing condition and the gestural conditions serves to explicate differences between a "gestural" system that functions as a linguistic system (ASL) and gestural systems that exist outside the linguistic domain. These findings are compatible with the hypothesis that left hemisphere specialization is not simply a function of motoric complexity or degree of symbolization but rather is attributable to inherent characteristics of human language.

Our results indicate that left hemisphere specialization honors a distinction between linguistic systems and nonlinguistic movement, even when expressed within the same manual modality. We have recently reported a case of a deaf signer (W.L.) with a left hemisphere lesion, which provides additional support for this view (*19*). W.L. demonstrates a global sign language aphasia with spared visuospatial abilities (*3*). However, unlike other left hemisphere–damaged signers, W.L. showed a highly unusual pattern, spontaneously substituting symbolic gestures (pantomime) for signs. Clinical tests reveal a sparing of pantomime production and pantomime comprehension, despite severe deficits in the production and comprehension of sign language. The differential disruption of linguistic gesture (sign) and symbolic gesture (pantomime) emphasizes the functional separability of sign language and gesture after left hemisphere lesion. This finding corroborates our experimental studies that suggest different patterns of lateralization for sign language and gesture in deaf individuals.

In summary, our experimental results indicate left hemisphere specialization of sign and spoken language in deaf and hearing persons skilled in these languages. In contrast, no evidence of hemispheric asymmetry was found for production of either symbolic or arbitrary gestures in hearing or deaf individuals. These findings are corroborated by the case study of a deaf signer who, after left hemisphere lesion, shows a well-preserved ability to use symbolic pantomimic gesture but who is severely aphasic for sign language. Taken together, this series of studies provides converging evidence for the linguistic specificity of left hemisphere dominance for language.

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