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A Functional Connection Between Inferior Frontal Gyrus and Orofacial Motor Cortex in Human

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Greenlee, Jeremy D. W., Hiroyuki Oya, Hiroto Kawasaki, Igor O. Volkov, Olaf P. Kaufman, Christopher Kovach, Matthew A. Howard, and John F. Brugge. A functional connection between inferior frontal gyrus and orofacial motor cortex in human. *J Neurophysiol* 92: 1153–1164, 2004. First published March 31, 2004; 10.1152/jn.00609.2003. The inferior frontal gyrus (IFG) of humans is known to play a critical role in speech production. The IFG is a highly convoluted and cytoarchitectonically diverse structure, classically forming 3 subgyri. It is reasonable to speculate that during speaking the IFG, or some portion of it, influences by corticocortical connections the orofacial representational area of primary motor cortex. To test the hypothesis that such corticocortical connections exist, electrical-stimulation tract tracing experiments were performed intraoperatively on 14 human subjects undergoing surgical treatment of medically intractable epilepsy. Bipolar electrical stimulation was applied to sites on the IFG, while the resulting evoked potentials were recorded from orofacial motor cortex, using a multichannel recording array. Stimulation of the IFG evoked polyphasic waveforms on motor cortex of both language-dominant and -nondominant hemispheres. The evoked waveforms had consistent features across subjects. The responses were seen in discrete regions on precentral cortex. Stimulation of motor cortex also evoked responses on portions of IFG. The data provide evidence for a functional connection between the human IFG and orofacial motor cortex.

INTRODUCTION

The complex neural circuits underlying human speech and language include areas of the frontal, temporal, and parietal lobes and their interconnections. Among these circuits is one, first postulated by Wernicke (1874) and later elaborated on by others, that is considered to be critically involved in speech perception and production (see Benson 1979; Benton 1994; Geschwind 1967, 1970; Stuss and Benson 1986). In its simplest form it includes the auditory receptive primary field (AI) on Heschl's gyrus, associational fields on temporal and parietal cortex, a premotor speech motor area on the inferior frontal gyrus (IFG), and, as part of a final common pathway for speech, the orofacial primary motor area on the precentral gyrus. It is further postulated that these areas are serially connected by a system of corticocortical pathways. Knowing the locations, functional organizations, and connectivity patterns associated with these areas is thus crucial to our understanding of cortical mechanisms underlying speech reception and production.

Using electrophysiological recording and stimulation methods, we described previously what we interpret to be in humans the primary auditory field on mesial Heschl's gyrus as well as a functionally distinct auditory association area (PLST) on the posterior lateral aspect of the superior temporal gyrus (Howard et al. 1996, 2000). We have mapped the functional connection(s) between these two fields (Brugge et al. 2003) and have presented additional evidence that area PLST makes a functional connection with the IFG as well (Garell et al. 1998). In the present work we have turned attention to the last link in this corticocortical chain, that is, the functional connectivity between the IFG and the orofacial motor representational area of the precentral gyrus.

The IFG is a highly convoluted gyral complex bounded by the inferior frontal sulcus dorsorostrally, the lateral fissure ventrally, and the precentral sulcus caudally. It is traditionally described as being divided by the anterior horizontal and ascending rami of the lateral fissure into 3 portions: pars orbitalis, pars triangularis, and pars opercularis. From the time of Broca (1861) the integrity of the IFG has been considered essential for normal speech and language function (Damasio and Geschwind 1984; Geschwind 1970; Stuss and Benson 1986). Electrical stimulation of the IFG of the dominant hemisphere leads to speech arrest (Lesser et al. 1984; Ojemann 1979; Ojemann and Whitaker 1978; Penfield and Rasmussen 1950; Penfield and Roberts 1959; Rasmussen and Milner 1975), and functional imaging studies have shown this area to be active during phonation (reviewed by Bookheimer 2002; Poeppel 1996). The classic Broca's speech area appears to occupy mainly pars opercularis and pars triangularis (reviewed by Amunts et al. 1999), which are associated with Brodmann's areas 44 and 45, respectively (Amunts et al. 1999; Petrides and Pandya 1994, 2001). There is, however, considerable intersubject variability in the macro- and microscopic anatomy of the IFG (Amunts et al. 1999), which creates some ambiguity in interpreting the relationships between the anatomical structure of the IFG and language deficits associated with IFG lesions (see Damasio and Geschwind 1984). There is also a high degree of intersubject variability in the exact locations where speech is disrupted by electrical stimulation, and frontal lobe language-critical sites have even been mapped outside this classical Broca area (Lesser et al. 1984; Ojemann 1992; Penfield and Roberts 1959). In addition, these language critical sites, when found, are not uniformly distributed but instead seem organized in mosaics of 1–2 cm^2 areal extent, often with sharp boundaries (Ojemann 1992). Despite intersubject variability and mosaic organization there seems to be a portion of

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the IFG immediately in front of the motor strip, perhaps even smaller than the classic Broca's area, which is essential for language in the vast majority of patients who are left brain dominant (Ojemann 1979, 1992).

The orofacial motor representation on the precentral gyrus in humans lies directly caudal to the IFG cortex with which it is presumably functionally connected. Electrical stimulation in this precentral motor cortex results in orofacial movements, vocal fold adduction, and vocalization responses (Foerster 1931, 1936; Penfield and Boldrey 1937; Penfield and Rasmussen 1950; Uematsu et al. 1992; Woolsey 1979). Disruption of motor mechanisms of speech (e.g., speech arrest) may also be elicited by stimulation in this region (Penfield and Rasmussen 1950). Bilateral lesions in the laryngeal representational area result in loss of voluntary control of phonation (see Mao et al. 1989). Thus it is postulated that this precentral motor area is involved in speech production and, moreover, that during speaking it engages the speech-critical areas of the IFG, presumably by way of corticocortical connections.

In monkey, the homologs of Brodmann's areas 44 and 45 are found in ventrolateral precentral cortex (Petrides and Pandya 1994, 1999, 2001). Cortex in the posterior bank of the lower limb of the arcuate sulcus exhibits characteristics resembling those of human area 44, whereas the area having characteristics similar to those of human area 45 occupies the rostrally adjacent periarcuate cortex. Orofacial motor cortex in monkey lies just caudal to these fields, on the inferior precentral gyrus, where electrical stimulation results in orofacial movement, including vocal fold adduction, though without vocalization (Hast 1966, 1974; Simonyan and Jurgens 2002; Sugar et al. 1948; Walker and Green 1938; Woolsey et al. 1952). The periarcuate and orofacial areas in monkey have been shown by anatomical and electrophysiological methods to be connected with each other as well as with numerous other cortical fields of the frontal, parietal, and temporal lobes (Deacon 1992; Godschalk et al. 1984; Petrides and Pandya 1999; Simonyan and Jurgens 2002; Tokuno et al. 1997). These findings in monkey give reason to believe that similar connectivity patterns may be found in humans as well.

The anatomical tracer methods used so effectively in revealing these corticocortical connections in monkey cannot be used in the living human brain. Carbocyanine dyes can be traced for only short distances, about 4–7 cm, in human postmortem brain tissue (Galuske et al. 1999, 2000; Sparks et al. 2000; Tardif et al. 2001), and thus are probably not useful for studying connections linking IFG and precentral gyrus, which likely exceed this distance. An alternative method—electrical stimulation tract tracing—has been used successfully in laboratory animals where the results have been corroborated by combining invasive electrophysiological recording and stimulation with anatomical tract tracing (Bignall 1969; Catsman-Berrevoets et al. 1980; Godschalk et al. 1984; Hyland et al. 1986; Waters et al. 1982). Electrophysiological tract tracing has proven to be a safe and effective method of identifying functional connections in the living human brain (Brugge et al. 2003; Howard et al. 2000; Liegeois-Chauvel et al. 1991; Rutecki et al. 1989; Wilson et al. 1990, 1991). This approach has its limitations, of course, because it provides no direct information on the cellular origins, anatomical trajectories, or terminal arborations associated with neural pathways. On the other hand, it provides information directly in the living brain on the functional connectivity between the site of electrical stimulation and the site(s) of recording. We have adopted this approach and by applying it systematically in epilepsy surgery patients have discovered functional connectivity between the IFG and orofacial motor cortex in humans.

METHODS

Electrophysiological experiments were conducted on 14 human subjects (7 males, 7 females, 20–54 yr, mean 38.7 yr) undergoing surgical treatment of medically intractable epilepsy. All subjects had temporal lobe epilepsy without demonstrable frontal lobe involvement. Data were acquired in the operating room during epilepsy surgery while clinically necessary intraoperative electrocorticographic sessions were ongoing. During data acquisition 10 subjects were awake under local anesthesia, whereas 4 others were under general anesthesia. Eight left and 6 right hemispheres were studied. Cerebral dominance for speech was determined by preoperative sodium amytal (WADA) testing (Wada and Rasmussen 1960). In 6 left and 5 right hemisphere cases the left hemisphere was language dominant. In 2 left and one right hemisphere cases WADA testing demonstrated bilateral language representation.

All subjects were evaluated extensively before surgery as part of the clinical treatment protocol. The evaluation included detailed neurological examination, routine blood tests, and high-resolution magnetic resonance imaging (MRI) of the brain. Cortical activity was assessed with scalp electroencephalography (EEG), and PET and/or single photon emission computed tomography (SPECT) in all subjects. These studies were performed only for the purpose of determining ictal and interictal patterns of cortical activity related to the subjects' epilepsy disorder. No subject showed evidence of frontal lobe dysfunction. Neuropsychological evaluation revealed language and behavioral performance in the normal range.

A craniotomy exposed the orofacial representational area of motor cortex and variable amounts of the IFG, most often the posterior portion including pars triangularis and pars opercularis. The most anterior portion of pars orbitalis was not exposed in any of the subjects. The clinical recording sessions were usually 30 min in duration and were undertaken to further clarify the anatomical source of epileptic activity and to guide the extent of resection. Two intraoperative clinical recording sessions were carried out in most patients. All subjects gave written informed consent before participation. All protocols were approved by the University of Iowa Institutional Review Board. Patients did not incur additional medical risk by participating in this protocol.

Electrical stimulation brain mapping

Electrical stimulation brain mapping is commonly carried out in neurosurgical patients at the time of operation to identify the patient's motor, sensory, and language-critical cortices using standard methods (Ojemann 1998). The method involves observing the patient's motor or sensory response to a brief train (50 Hz) of pulses (0.2 ms duration) applied to the cortical surface. Following this standard methodology, electrical-stimulation brain mapping was performed using a handheld bipolar stimulating electrode and a Grass SD9 (Grass-Telefactor, West Warwick, RI) constant-voltage stimulator. Response threshold was typically 10 V at 50 Hz. Stimulus strengths of $\geq$10 V are used routinely for clinical mapping. Electrocorticographic monitoring showed that this stimulus did not evoke after-discharges.

Responses to stimulation of precentral motor cortex were obtained in 9 of the 10 subjects that were awake at surgery. Because of time constraints the orofacial region was not mapped systematically and the patients were not asked to provide detailed descriptions of their experiences elicited by electrical stimulation. The aim was to confirm that the cortical area under study represented the orofacial region.

Response to precentral motor cortex stimulation took on a variety of forms. Commonly orofacial motor cortex stimulation elicited contractions of the tongue and contralateral face. In one case stimulation caused the pitch of the patient's ongoing vocalization to change, which we interpret as resulting from disruption of vocal fold function. Language-critical cortical sites in the IFG were identified in 2 of the 5 awake subjects undergoing stimulation mapping in the language-dominant hemisphere. In one subject arrest of counting was observed during stimulation of cortex immediately anterior to the ventral-most portion of the precentral gyrus at the junction with the posterior, inferior portion of pars opercularis (L79, Fig. 4). In the second subject (L91, Fig. 7), naming errors were seen on stimulation of the superior, anterior portion of pars opercularis. There are several possible reasons why language-critical sites were not routinely identified within the IFG. The craniotomy exposure precluded access to the full anterior extent of the IFG where language-critical sites may have been located. Also, language-critical sites may have been located on fissural walls (Amunts et al. 1999) and thus beyond the reach of our stimulating electrodes. There is individual variability in language localization (Ojeman 1979, 1989) and, without a detailed and systematic mapping study of the entire gyral complex, language-critical sites simply may have been overlooked. Finally, in some cases the stimulus intensity may not have been sufficient to disrupt language function. We did not explore systematically the effects of changing stimulus level. Once the sites on precentral gyrus and IFG were identified for further study a recording grid was put in place and electrical stimulation tract tracing begun. The stimulus parameters used in tract tracing differed from those used for electrical stimulation mapping.

Electrical stimulation tract tracing

Electrical stimulation tract tracing is a safe and effective investigative tool used in humans and laboratory animals to examine functional connections between brain sites. An electrical impulse is applied to one brain location and resulting stimulus-evoked potentials are searched for and recorded at distant sites (Bignall 1969; Howard et al. 2000; Liegeois-Chauvel et al. 1991; Pearce et al. 2000; Rutecki et al. 1989; Wilson et al. 1990, 1991). In the present study electrical-stimulation tract tracing was carried out using a custom-made bipolar stimulating electrode whose tips were silver balls approximately 2 mm in diameter and 2 mm apart. Guided by the results of electrical stimulation mapping, the tips were brought into contact with the cortex, the assembly was firmly clamped in position at each stimulating location, and a photograph was taken to document the anatomical placement. A Grass SD-9 constant-voltage stimulator was used for 12 experiments. This produced a single charge-balanced pulse of 0.2 ms duration with a fixed interstimulus interval of 2 s. A Grass S12 constant-current stimulator was used for 2 subjects. This produced a 0.2-ms biphasic square wave. At each stimulus location, responses to 30 to 50 stimuli were recorded for averaging. In most cases polarity was reversed for half the stimuli in an effort to minimize stimulus artifact. Unlike trains of pulses, single pulses elicit neither a sensory nor a motor response.

Responses evoked by cortical electrical stimulation were recorded using a custom-manufactured, 64-contact, 8×8 electrode array. The silver electrode contacts were 0.63 mm in diameter with a center-to-center separation of 3 mm. After positioning on the cortical surface, the recording array was firmly fixed to the patient's skull and a photograph taken of its location. A subgaleal platinum electrode located near the vertex served as the reference electrode. Potentials were amplified with a gain of 5,000 (Grass Model 15 amplifiers) and band-pass filtered on-line (1–6,000 Hz). Sampling frequency was 8 or 10 kHz. Waveforms were digitized on-line (Hewlett Packard VX-1 data-acquisition system) and stored for off-line analysis. In most subjects it was possible to obtain data from stimulation of several sites on the IFG. In some subjects the paradigm was reversed and motor cortex was stimulated electrically while recordings were obtained from IFG.

Commercially available and custom-developed in-house software was used to analyze the averaged evoked potentials. Those epochs containing epileptic discharges or anomalous artifacts were discarded before averaging. Stimulation and recording sites were localized using a combination of 3D reconstruction of preoperative MRI images (Brainvox; see Frank et al. 1997) and high-resolution intraoperative digital photographs. We estimate the error in reconstructing the locations of the recording array and stimulating electrode on the brain surface to be about 1–2 mm.

RESULTS

The presence of secondary fissures and dimples coupled with variation in the course of the lateral fissure often obscures the classic tripartite structure of the IFG and leads to considerable anatomical variation in this area from one brain to the next, as was the case among the 14 subjects in our study (see also Amunts et al. 1999). A prototypic configuration of the tripartite structural arrangement of the IFG is illustrated in Fig. 1*A* by a 3D MRI taken of one of our subjects. Figure 1, *B–D* presents 3D MRIs taken of the brains of 3 additional subjects in our study showing the extent of departure from this classic structure. We emphasize here this intersubject anatomical variability in IFG cortical anatomy because it led to difficulties in specifying precisely the stimulation and recording locations in a manner that could be generalized across all of our subjects.

Waveforms recorded on motor cortex after electrical stimulation of IFG

The recording locations on precentral cortex were typically confined to that region of the precentral gyrus ventral and posterior to the level of the termination of the inferior frontal sulcus in the precentral sulcus. Electrical stimulation mapping in the awake subjects confirmed that this region of the precentral gyrus was orofacial motor cortex (see Figs. 2*A*, 4*A*, 5*A*, 6*A*, 8, *A* and *B*) in agreement with previous reports (Foerster 1936; Penfield and Boldrey 1937; Uematsu et al. 1992; Woolsey 1979).

A complex waveform was evoked on orofacial motor cortex in response to electrical stimulation of the IFG. The recordings shown in Fig. 2 were made on the rostral edge of the precentral sulcus where the evoked potential (EP) having the maximal response amplitude was observed (Fig. 2*A*, asterisk). This site was about 1 cm anterior to the region where direct 50-Hz electrical stimulation resulted in mouth and jaw movement. The bipolar stimulus was applied to what we interpret to be the ventral portion of pars triangularis. The averaged evoked response on motor cortex to a single electrical stimulus applied to this area of the IFG was a triphasic waveform occurring within 100 ms after stimulation. This waveform consisted of an initial small positive deflection followed in turn by a large negative and a broader positive deflection. [Negative potentials are depicted as upward deflections.] Beyond 100 ms an even broader negative deflection was occasionally recorded as well (see Fig. 3). Major deflections are referred to as P1, N1, and P2 to indicate deflection polarity in order of appearance. In this experiment, response threshold was reached when the stimulus strength was between 5 and 10 V. In Fig. 2*B* vertical dashed lines mark the peak latency of P1, N1, and P2 obtained at

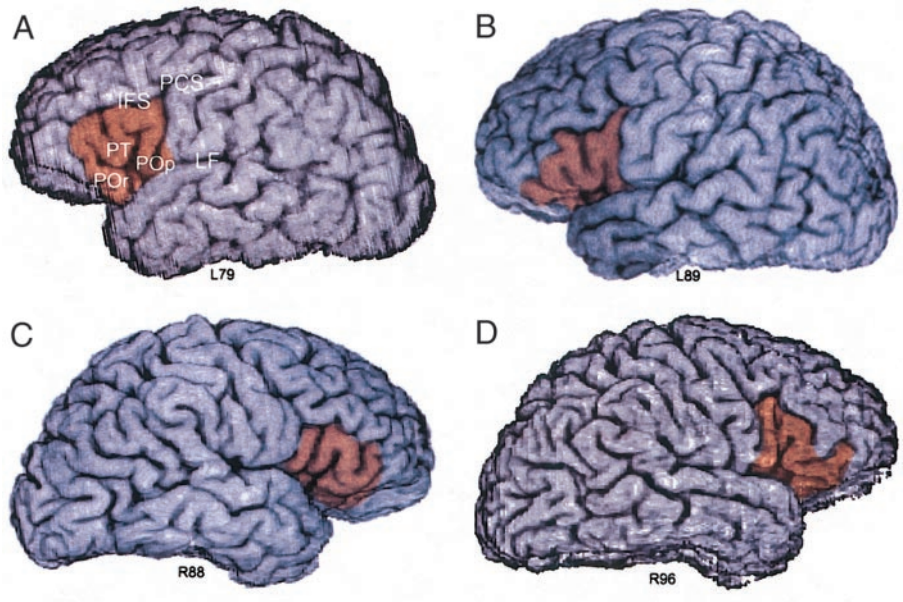


FIG. 1. Lateral 3D brain MRI reconstructions of 4 experimental subjects. *A*: classical configuration of 3 subgyri in the inferior frontal gyrus (IFG) (shaded in orange) and the sulci demarcating the IFG. *B–D*: variability in the gross anatomic configuration of the IFG. PCS, precentral sulcus; LF, lateral fissure; POp, pars opercularis; PT, pars triangularis; POr, pars orbitalis.

stimulus strength of 10 V where the waveform was first clearly defined. As stimulus strength was raised further there was a small but systematic shortening in the peak latency of each of the 3 major deflections. In this example, the latency of the early positive (P1) deflection shifted from 12.2 ms at near-threshold stimulus intensity to 10.5 ms at the highest intensity used. Comparable shifts were seen for the other deflections as well. Latency shifts were accompanied by an initial growth in peak amplitude of each deflection. The negative deflection exhibited a nearly monotonic growth in amplitude over the range of stimulus strengths used, whereas P1 and P2 showed a leveling off, or even decrease, in amplitude at higher stimulus strengths (see Fig. 2*C*).

At comparable stimulus strength, the triphasic shape of the electrically evoked waveform recorded at the site of maximal amplitude of response on the orofacial motor area of the precentral gyrus was remarkably consistent across subjects, although the latencies of the peaks could vary considerably. Figure 3*A* shows EPs recorded in 6 different subjects illustrating this waveform consistency. The peak latencies for each of

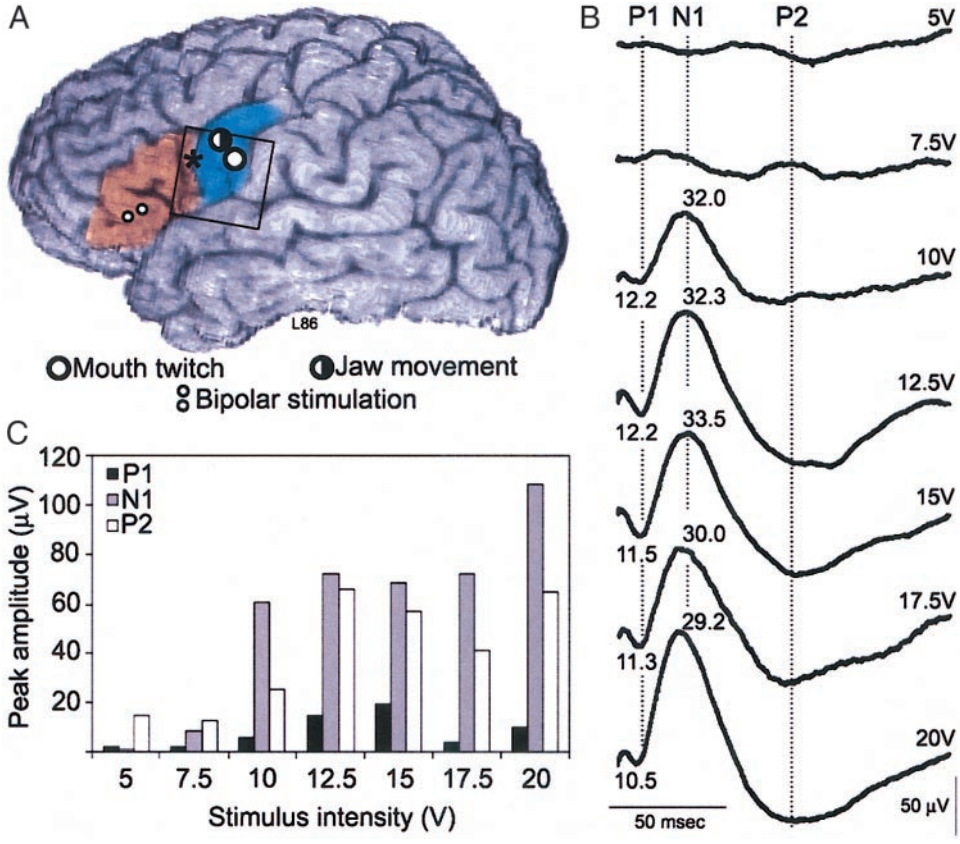
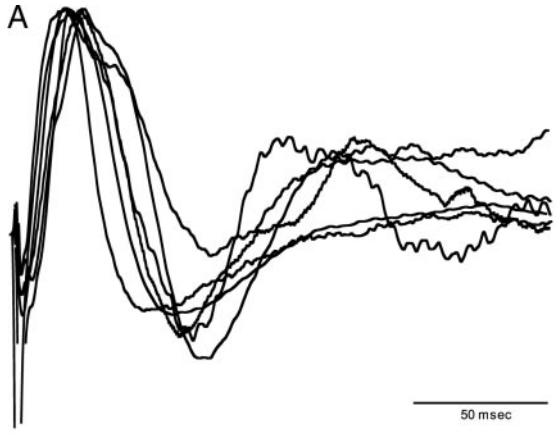


FIG. 2. *A*: lateral MRI reconstruction demonstrating the IFG (orange), motor cortex (blue) as confirmed by electrical stimulation mapping (large black and white circles), site of stimulation on IFG for tract tracing (small black and white circles), position of recording array (black box; 25-mm square), and site of maximal response (asterisk). *B*: averaged waveforms from the electrode denoted by the asterisk showing 3 components (P1, N1, P2) and increasing amplitude and shift in latency with increasing stimulus intensity. Latency shown in ms. *C*: bar graph for the amplitude of the 3 components vs. stimulus intensity demonstrating a response threshold near 10 V. Decrease in amplitude of P1 at higher intensities may be related to increased amplitude of N1.

A



B

Subject	P1	N1	P2
L79	--	25.0	62.3
R80	--	20.7	73.2
L81	--	24.0	62.5
L85	3.3	16.2	55.0
L86	3.3	19.2	66.2
L90	5.8	25.0	69.6
L91	5.7	19.1	65.5

FIG. 3. *A*: superimposed, normalized waveforms for the site of maximal response on precentral cortex after stimulation of IFG for 6 different subjects. P1 is partially obscured by stimulus artifact in some cases. *B*: component latency for 6 waveforms depicted above demonstrating intersubject variability.

the major deflections are given in Fig. 3*B*. Across all subjects studied, P1 peaks occurred as early as 2.8 ms and as late as 12.2 ms, with the majority occurring around 7 ms. The onset latency of P1 measured in those few cases not obscured by stimulus artifact ranged from 2.6 to 6 ms. Those deflections that occurred later than 20 ms were affected to a lesser degree by the stimulus artifact. N1, P2, and the later negative deflections also showed latency variation within and across subjects. The overall range of N1 latency was 15–32 ms, and that of P2 latency was between 50 and 82 ms. The later broad negative deflection evident in some of the waveforms (e.g., Fig. 3*A*) exhibited latencies ranging between 100 and 190 ms. These relatively large ranges of latency found within or across subjects were possibly attributable to the fact that our stimulus-recording paradigms included a number of variables that we were unable to control, considering the brief time available to us (~30 min) for carrying out these studies in the operating room. Most important, perhaps, we were unable to map the active stimulation sites on the IFG with as fine a spatial grain as would be desirable. This led, for example, to the situation where in the same subject (L86) the latencies exhibited by waveforms illustrated in Fig. 2*B* differed substantially from those shown in Fig. 3*B*. In this case the recording site was the same but the stimulation sites on IFG differed. In all but a few cases we were unable to study in a parametric fashion the intensity sensitivity at each recording and stimulation site, and thus we did not have an accurate estimate of response threshold, which as shown above could affect latency.

We interpret these electrically evoked responses as reflecting underlying net synaptic currents created by afferent input arriving over a connection between IFG and orofacial motor cortex. We further interpret the earliest component, P1, as the sign of first afferent invasion of motor cortex. The precentral sulcus is a deep fissure, and the length of axons connecting the IFG to the precentral gyrus are estimated to be ≥6–8 cm in length based on measurements from the MRIs of these subjects. From consideration of these transmission distances and of the onset (2.6–6.0 ms) and peak (2.8–12.2 ms) latencies of P1 we estimate that the conduction velocity of axons in this presumed corticocortical pathway would be around 10–30 m/s.

Response fields on motor cortex to stimulation of IFG

The responses evoked on the ventral precentral gyrus by focal electrical stimulation of IFG were largely confined to small portions of the confirmed orofacial motor cortex. We refer to these regions within which EPs aggregate as *response fields*. For the series as a whole we found response fields on precentral gyrus resulting from stimulation of each of the 3 major subdivisions of the IFG.

Figure 4 illustrates one such response field that was confined largely to an area on the ventral aspect of the precentral gyrus around the lateral fissure where direct 50-Hz stimulation resulted in speech arrest. The bipolar electrical stimulus was applied to a site on the rostral portion of what we interpret to be the anterior limb of pars triangularis, with one contact of the bipolar pair resting slightly rostral to the tip of the ascending limb of the lateral fissure. Whereas the location of this response field was clearly correlated with the location of a speech arrest site, no clear EPs were seen in the area dorsal to it on the precentral gyrus where 50-Hz stimulation led to jaw movement and speech arrest. Of course, if we had the time to more systematically explore the IFG with a stimulating electrode we may have found other sites that activated these other orofacial regions of precentral gyrus.

Although we recorded response fields in orofacial motor cortex in all subjects studied, during any given experiment not all IFG stimulation sites were effective in activating that region of precentral motor cortex covered by the recording grid, at least not at the stimulus strengths used. Figure 5 illustrates this finding in another subject. In this subject, motor cortex recordings were obtained after stimulation of 3 different sites on the IFG and of one site just dorsal to the IFG on the middle frontal gyrus. Stimulation of only one of these sites resulted in evoked activity on orofacial motor cortex. The anatomical structure of the IFG in this subject departed from the classic tripartite division and thus some ambiguity was created as to the appropriate anatomical specification of 3 of the 4 stimulation sites. We tentatively localize the effective stimulus site to caudal pars triangularis and perhaps rostral pars orbitalis. Two ineffective sites were clearly on the IFG, possibly caudal pars triangularis. A fourth ineffective site appeared to be rostral and dorsal to the inferior frontal sulcus, although in this subject the sulcus was discontinuous. The response field resulting from stimulation of the effective IFG site, shown in Fig. 5*B*, was located somewhat more anteriorly and dorsally on the motor cortex than the one shown in Fig. 4. Nonetheless, this was the precentral orofacial representation, given that stimulation of this region resulted in lip and tongue movement or a change in pitch of a speech sound. Had we used a range of stimulus strengths at each stimulus site it is, of course, possible that we would have activated these otherwise nonexcitable sites. Taken together, however, the results suggest that the IFG-to-motor cortex functional connection may be topographically parcellated.

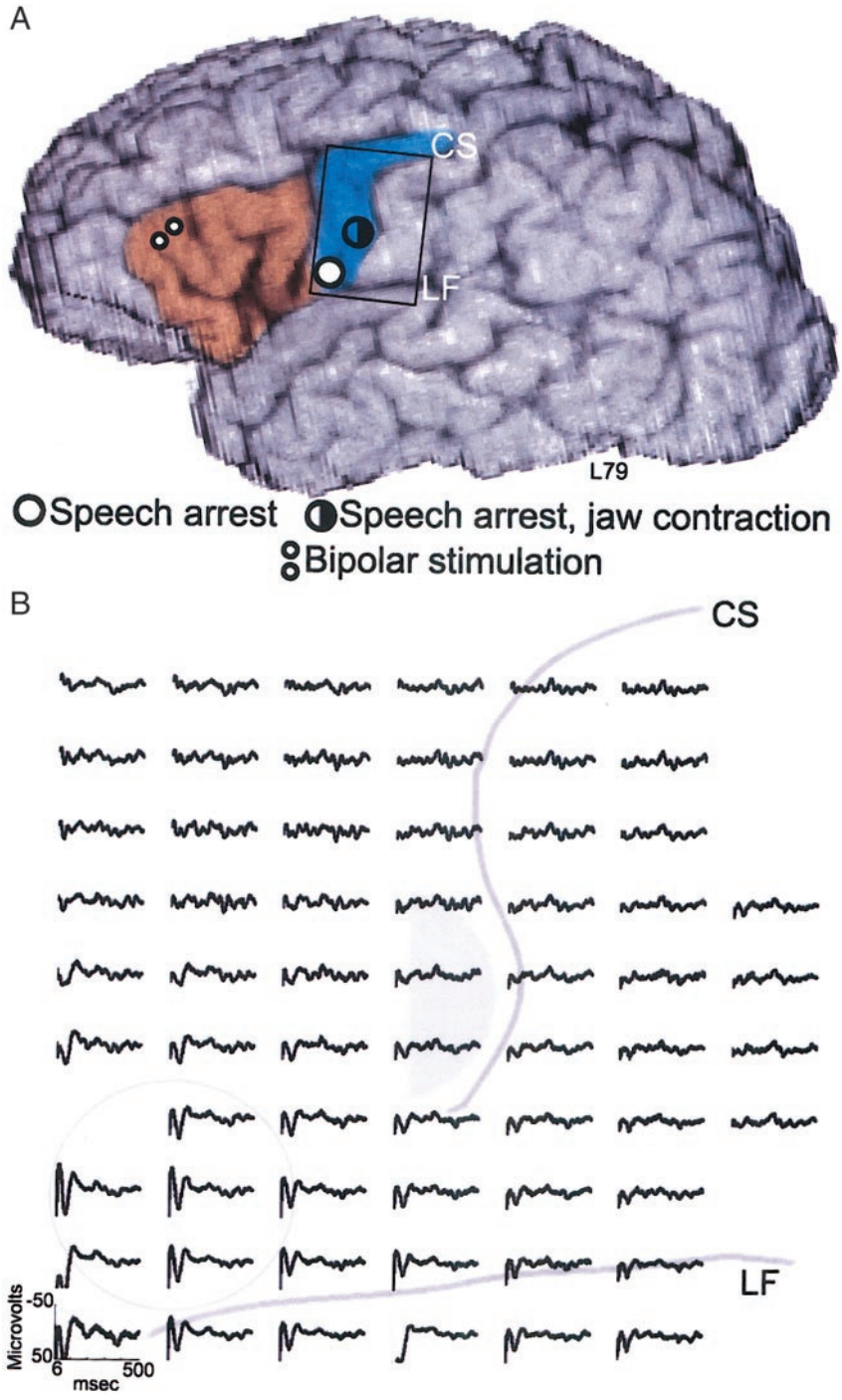


FIG. 4. *A*: lateral MRI reconstruction illustrating IFG (orange), motor cortex (blue), results of electrical stimulation mapping (large black and white circles), stimulation location during tract tracing (small circles), and position of recording array (black box; 22 × 31 mm). *B*: averaged evoked potentials (EPs) for 64-contact recording array showing a response field on the anterior, inferior corner of the array. Superimposed shaded circles represent the same results of electrical stimulation mapping as in *A*. Gray lines indicate sulci. CS, central sulcus; LF, lateral fissure.

We were unable to examine in the same subject the functional connection between IFG and motor cortex in both language-dominant and -nondominant hemispheres. Comparing data obtained from the 2 hemispheres in different subjects, however, we saw no obvious systematic differences in response fields or waveform morphology. One example, from a study of a right (nondominant) hemisphere, is illustrated in Fig. 6. As shown in Fig. 6*A*, the bipolar stimulating electrode tips were in contact with the most dorsocaudal portion of the IFG, possibly pars opercularis. Again the irregular anatomical configuration of the IFG in this case precluded specifying precisely the anatomical definition of this stimulus site. The resulting response field appeared to span the ventral aspects of ventral pre- and postcentral gyri, a region from which 50-Hz stimulation evoked movement of the mouth and tongue.

Response of IFG to electrical stimulation of precentral motor cortex

We tested in 4 subjects whether a functional connection also exists from precentral motor cortex to IFG. We did this by stimulating sites on orofacial motor cortex and recording resulting evoked activity on the IFG. Response fields on the IFG resulting from orofacial motor stimulation were relatively cir-

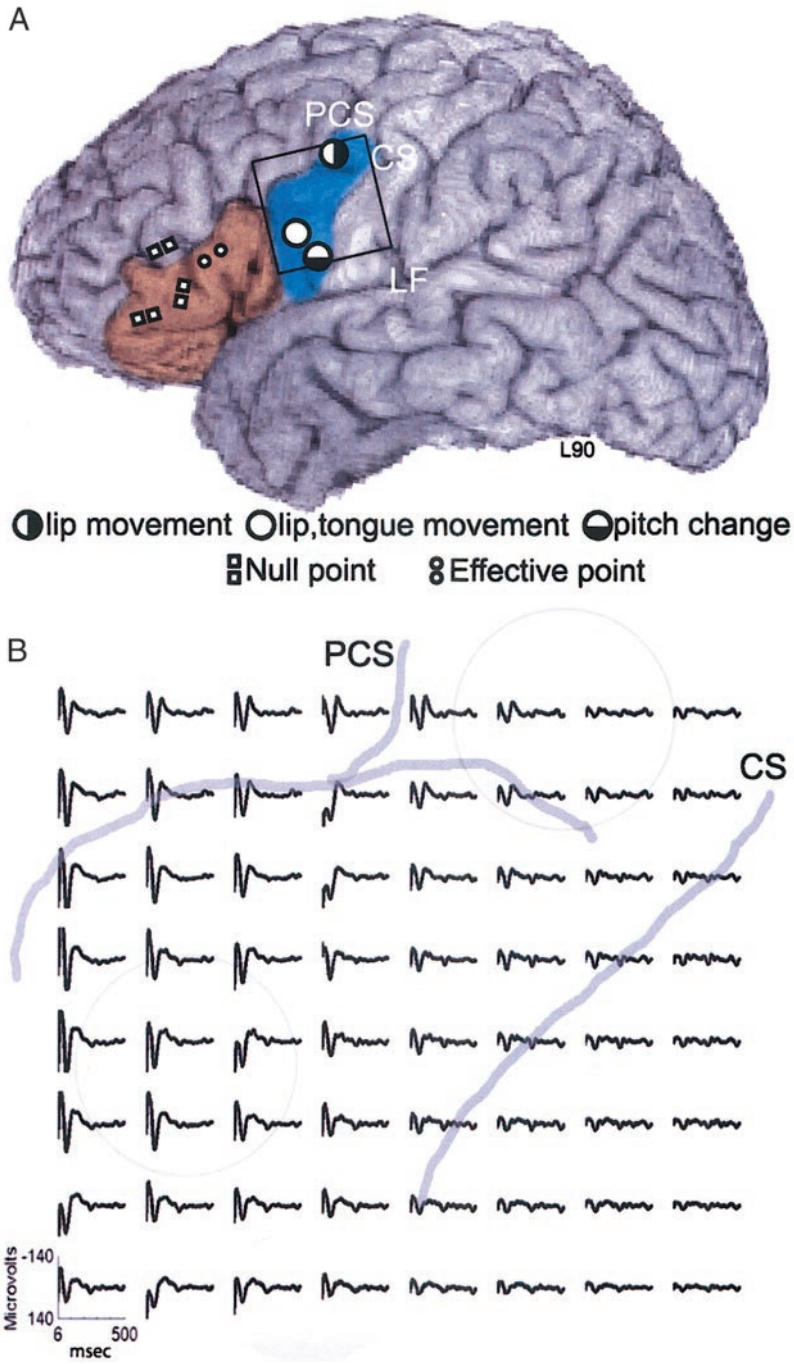


FIG. 5. *A*: lateral MRI reconstruction illustrating IFG (orange), motor cortex (blue), results of electrical stimulation mapping (large black and white circles), and position of recording array (black box; 25-mm square). Four different stimulation locations are shown: small squares indicate stimulus sites that did not evoke responses on motor cortex, and small circles indicate a site that evoked the responses depicted in *B*. *B*: averaged EPs for 64-contact recording array showing a response field on the precentral gyrus. Superimposed shaded circles correspond to the above results of electrical stimulation mapping. Gray lines indicate sulci. CS, central sulcus; LF, lateral fissure.

cumscribed and their locations were related to the location of the stimulating electrode on the precentral gyrus. Figure 7 illustrates findings from 2 subjects. In both cases response fields were recorded on inferior frontal cortex, but because of the irregular configuration of the IFG it was difficult to specify with certainty which anatomical subregion of the IFG contained the recording sites. In one case (Fig. 7*C*) a response field was clearly confined to the dorsoposterior aspect of the IFG, possibly the posterior limb of pars triangularis and/or pars opercularis (marked with a plus sign). Rostral to this response field a second area of evoked activity emerged on the dorsal and rostral portion of the recording grid and with waveforms different from those recorded in the more caudal field (marked with an asterisk). The map of Fig. 7*D* also shows the presence of possibly two response fields made up of different waveforms. One response field is represented by just a few active sites on the IFG near the center of the recording array (asterisk). The other is located ventrocaudally, just above the lateral fissure, possibly caudal to the precentral sulcus (plus sign). These waveform complexes recorded in the IFG differed from those recorded on motor cortex to IFG stimulation.

Figure 8 illustrates in greater detail the waveforms recorded from the 2 response foci for the 2 subjects illustrated in Fig. 7. Regardless of the recording or stimulation site, each waveform exhibited an early positive deflection followed by a series of negative and positive deflections. Figure 8*A* illustrates wave-

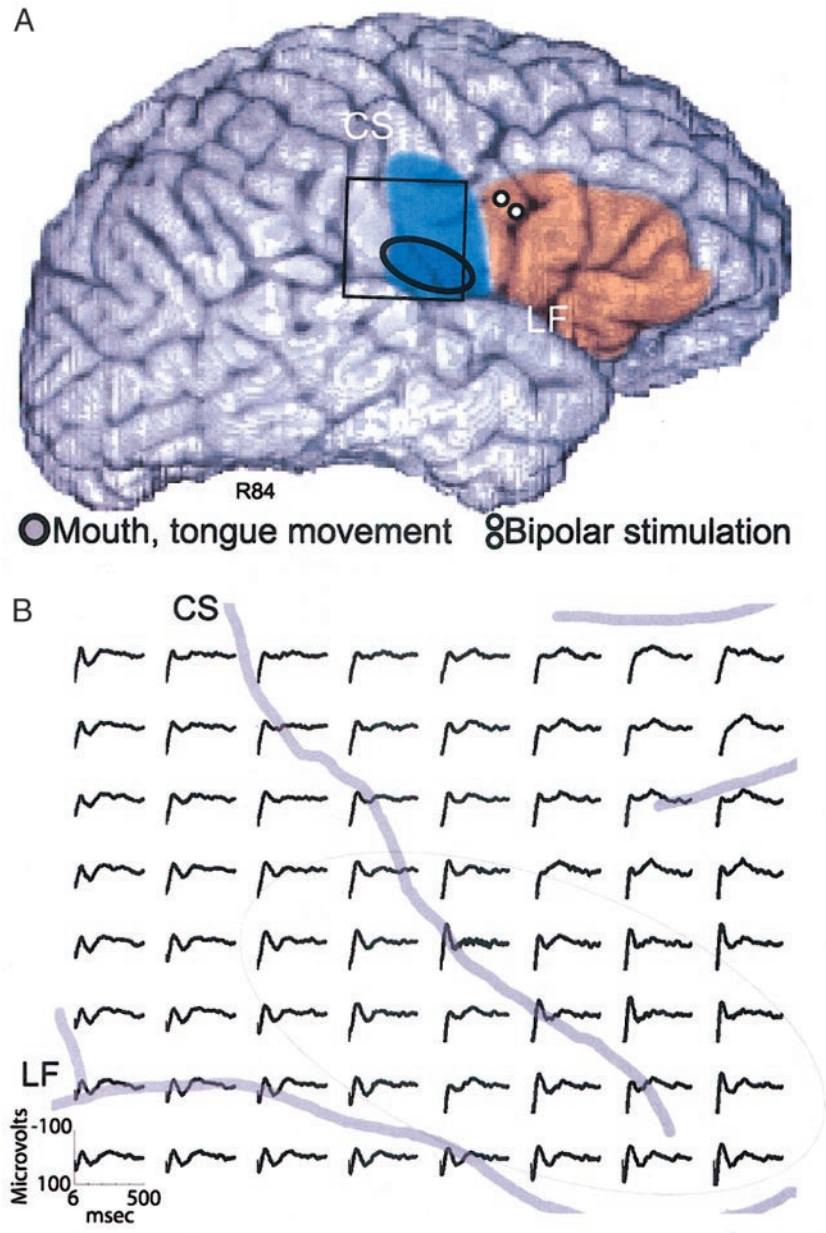


FIG. 6. *A*: lateral MRI reconstruction of a nondominant hemisphere showing an atypical IFG gross anatomic configuration (orange), motor cortex (blue) as identified by electrical stimulation mapping (black oval), and the position of the recording array (black box; 25- mm square) and stimulation point (black circles) during tract tracing. *B*: averaged EPs of similar morphology and latencies to experiments in the dominant hemisphere with the responses of maximal amplitude located within motor cortex (shaded oval). Gray lines indicate sulci. CS, central sulcus; LF, lateral fissure.

forms recorded at the 2 sites shown in Fig. 7*A*, whereas Fig. 8*B* shows waveforms recorded at the 2 sites marked on the map in Fig. 7*B*. In each subject these waveforms were recorded simultaneously, and thus waveform differences can be attributed to differences in underlying net synaptic activity. Differences shown in Fig. 8*B* are especially striking.

DISCUSSION

Two major findings have been presented regarding the functional connections between the IFG and orofacial motor cortex in humans. First, a single electrical stimulus applied to the IFG evokes polyphasic waveforms that aggregate to form response fields in the orofacial representational area of the precentral gyrus. We take these results as evidence for a functional connection between those IFG areas and orofacial motor cortex on the precentral gyrus. Second, the same stimulus applied to orofacial motor cortex results in response fields in IFG composed of waveforms having a different morphology. We interpret the presence of this evoked activity to mean that IFG and orofacial motor cortex are functionally connected in reciprocal ways.

A waveform recorded by an electrode on the brain surface varies in magnitude and polarity over time, depending on the timing, strength, and location of synaptic current sinks and sources in the vicinity of that electrode (see Arezzo et al. 1986; Mitzdorf 1985, 1991, 1994; Vaughan and Arezzo 1988). The response fields we recorded were often well localized within the recording array, and amplitude gradients of EPs within these fields were often steep between closely spaced neighboring recording sites. Hence, we interpret the electrically induced EP as reflecting the summation of ionic current flowing mainly within the cortex immediately beneath the recording electrode, created by the invasion of stimulus-evoked input arriving over one or more afferent pathways. However, in some cases we

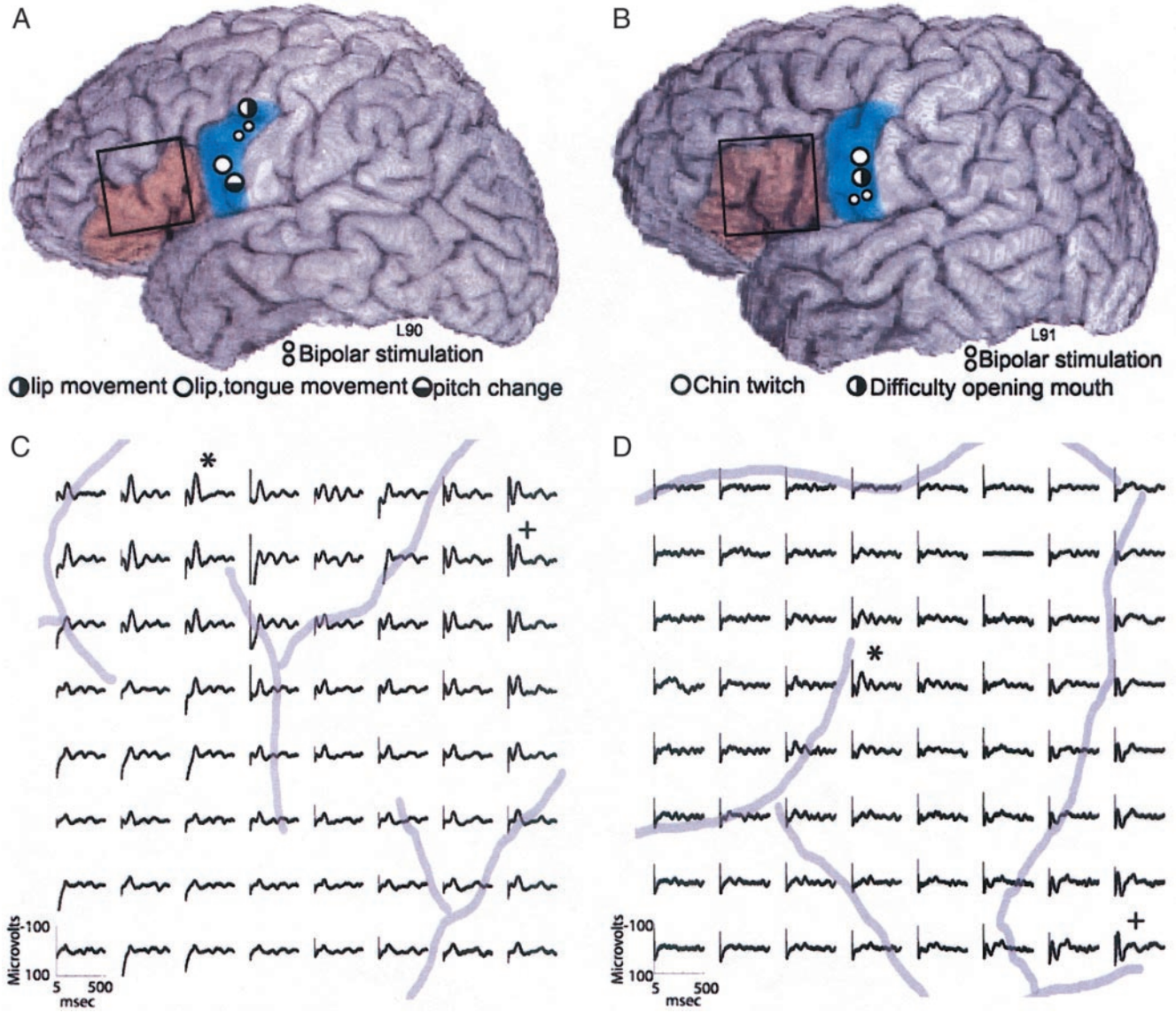


FIG. 7. *A* and *B*: lateral MRI reconstructions from 2 subjects showing the position of the recording array (black box; 25-mm square) on IFG (orange) and sites of tract tracing stimulation (small circles) on motor cortex (blue). Large black circles indicate the results of electrical stimulation brain mapping. *C* and *D*: averaged EPs for the 64 contact recording array after stimulation at the points illustrated in *A* and *B*, respectively. Two discrete response fields on each map are marked with an asterisk and plus sign.

cannot exclude possible contributions from nearby intrasulcal sources. Although not completely understood, a fast-rising rectangular pulse of depolarizing negative current is considered the most efficient waveform for extracellular stimulation, although extracellular anodal current can also be an effective stimulus (Yeomans 1990). Despite its drawbacks (see also Brown et al. 1973; Ranck 1975) we used a bipolar stimulus configuration to minimize the stimulus artifact. The fact that moving the stimulating electrode along the IFG cortical surface several millimeters often resulted in loss of stimulus-evoked responses on the precentral gyrus indicates that the spread of effective stimulation was relatively restricted.

If in the human connections made by the IFG are as widespread as those made by what might be considered homologous regions in monkey (Deacon 1992; Godschalk et al. 1984; Petrides and Pandya 1999; Simonyan and Jurgens 2002; Tokuno et al. 1997) then we need to consider our results as possibly pointing to both direct and indirect corticocortical projections from IFG to motor cortex. Some clue as to the nature of the connection may be derived from the structure of the evoked waveform. The earliest deflections of the EP exhibit a latency of $<$13 ms, which is consistent with a direct corticocortical projection. The fact that latency of this wave shortens with increases in stimulus strength suggests orthodromic synaptic activation. We estimate from the onset and peak latency of this early wave, and from the measured distance between stimulus and recording sites, that the conduction velocity in a pathway connecting directly the IFG and motor cortex to be 10–30 m/s. In rabbit, Swadlow (1994) has shown conduction velocities of corticocortical neurons in motor, sensory, and visual cortex to be $<$3 m/s, suggesting a mixture of fine-diameter myelinated and nonmyelinated axons. He also reported, however, layer 5 efferents as having axonal conduction velocities of 10–15 m/s. In visual cortex of the rhesus

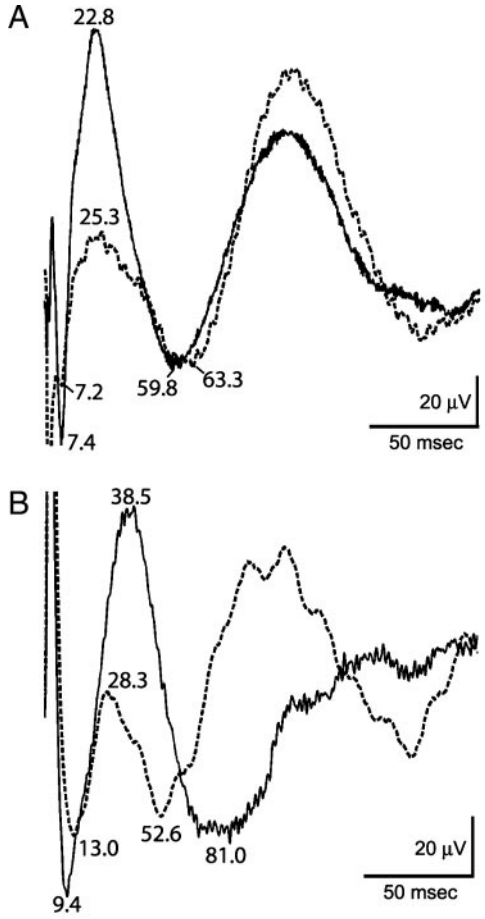


FIG. 8. Superimposed waveforms from 2 recording sites of maximal amplitude responses obtained on IFG of 2 subjects in response to stimulation of precentral motor cortex. Solid line refers to waveform marked with asterisk on maps of Fig. 7, dashed lines to waveforms marked with plus sign. Latency of each major peak shown.

monkey, callosal fibers were found to have conduction velocities of 2–20 m/s (Swadlow et al. 1978). Little is known about fiber size and conduction velocities of the human frontal lobe. A single microscopic study of 3 human frontal lobe specimens showed the majority of fibers are 1–4 μm in diameter (Bishop and Smith 1964). Assuming that this fiber size applies to myelinated axons of IFG projection neurons our estimated conduction velocity of 10–30 m/s leads us to a plausible conclusion that a direct connection exists between IFG and motor cortex.

This interpretation is consistent with the findings of Godschalk et al. (1984), who showed in the rhesus monkey that antidromic EP and single-unit responses are recorded from postarcuate cortex, the presumed homolog of human area 44 on pars opercularis (Amunts et al. 1999; Petrides and Pandya 1994), in response to intracortical electrical stimulation along the precentral gyrus. Thus if our interpretation is correct the results provide evidence for a connection from inferior frontal cortex to motor cortex, as hypothesized in the so-called Wernicke–Geschwind model. Moreover the data indicate that in human, as in monkey (Goldschalk et al. 1984), this is a rapid pathway for premotor input to motor cortex. Interpretation of the source(s) of later deflections in the evoked waveform is necessarily more speculative. Considering the relatively long latency to the peaks of the large negative and later positive deflections we might speculate that these represent activity arriving over longer, slower conducting, multisynaptic pathways that may originate in IFG. It may be of some interest to note in this regard that, in monkey, electrical stimulation of the posterior wall of the arcuate sulcus yields combined activity in both the thryoarytenoid and cricothyroid muscles with average latencies of 20–40 ms. These intrinsic laryngeal muscles act synergistically during phonation to regulate vocal fold tension and length (Hast et al. 1974).

In those cases where multiple sites on IFG were stimulated, only a subset of those sites were effective in eliciting evoked responses on motor cortex. These results suggest that not all of the IFG cortex makes functional connections with the precentral gyrus, but that the connection is topographically parcellated. Suggestions of such functional parcellation of the IFG have been made by others based on studies using electrical brain stimulation (Ojemann 1983), fMRI (Binkofski et al. 2000; Paulesu et al. 1997), MEG (Dhond et al. 2001; Sasaki et al. 1995), PET (Blank et al. 2002; Hsieh et al. 2001; Petersen et al. 1988), and cytoarchitectonics (Binkofski et al. 2000). Unfortunately, the intersubject variability of gross anatomical features of the IFG coupled with inconsistent spatial relationships between sulcal features, underlying cytoarchitecture and physiologically defined cortical fields makes systematic comparison of functional localization between subjects difficult.

The current report provides the first experimental evidence for a projection from IFG to precentral orofacial motor cortex in humans. A small deflection having an onset latency of 2.8–6 ms indicates that at least a portion of this functional connection is direct, a finding that is consistent with observations of Goldschalk et al. (1984) in monkey that injections of HRP into the inferior limb of the arcuate sulcus resulted in retrogradely labeled cells in precentral gyrus. An additional observation from our experiments is of note: stimulation of a small region of orofacial motor cortex resulted in 2 response fields appearing on the IFG, separated in space and made up of waveforms that differ from each other. This suggests that in these cases electrical stimulation activated 2 projection pathways that arose from a common source on motor cortex and terminated in 2 different regions of the IFG. More data are needed to substantiate our finding that the waveforms recorded on IFG to stimulation of motor cortex differ in their morphology from those recorded on motor cortex when IFG is stimulated. This would suggest that the projection pathway(s) from motor cortex to IFG might differ from those originating in IFG and ending in motor cortex. Our sample is relatively small and further research is needed to understand better how these pathways are functionally integrated into the complex mechanisms that are engaged during the speech process.

The periarcuate region in monkey is polysensory in nature, receiving auditory, somatic sensory, and visual input from respective temporal, parietal, and occipital associational cortical fields (e.g., Bignall et al. 1969). These areas project in turn on motor cortex. Consistent with these monkey findings, we previously showed that in humans an auditory association field on temporal cortex sends a functional projection to the IFG (Garell et al. 1998), and we now have provided evidence in human for a functional projection to orofacial precentral motor cortex. It would appear that, like the monkey (Tokuno et al. 1997), the human IFG may play a role in integrating auditory,

somatic, and visual information in the control of vocal and oral movement systems. Just how this system interacts with other frontal lobe areas in speech motor control is yet to be determined.

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