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Functional Connections Within the Human Inferior Frontal Gyrus

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ABSTRACT

The highly convoluted and cytoarchitectonically diverse inferior frontal gyrus (IFG) of humans is known to be critically involved in a wide range of complex operations including speech and language processing. The neural circuitry that underlies these operations is not fully understood. We hypothesized that this neural circuitry includes functional connections within and between the three major IFG subgyri: the pars orbitalis, pars triangularis, and pars opercularis. To test this hypothesis we employed electrical stimulation tract-tracing techniques in 10 human patients undergoing surgical treatment for intractable epilepsy. The approach involved delivering repeated bipolar electrical stimuli to one site on the IFG while recording the electrical response evoked by that stimulus from a 64-contact grid overlying more distant IFG sites. In all subjects, stimulation of a site on one subgyrus evoked polyphasic potentials at distant sites, either on the same subgyrus or on an adjacent subgyrus. This provided prima facie evidence for a functional connection between the site of stimulation and the sites of the evoked response. The averaged evoked potentials tended to aggregate as response fields. The spatial spread of a response field indicated a divergent projection from the site of stimulation. When two or more sites were stimulated, the resulting evoked potentials exhibited different waveforms while the respective response fields could overlap substantially, suggesting that input from multiple sites converged but by engaging different neural circuits. The earliest deflection in the evoked potential ranged from 2 to 10 msec. No differences were noted between language-dominant and language-nondominant hemispheres. J. Comp. Neurol. 503:550–559, 2007.

Indexing terms: Broca's area; areas 44, 45, 47/12; electrical stimulation; brain mapping; language; surgery

The inferior frontal gyrus (IFG) in humans lies ventral to the inferior frontal sulcus, anterior to the precentral sulcus, and superior to the lateral (Sylvian) fissure (LF). It is subdivided by the anterior ascending (AAR) and anterior horizontal (AHR) rami of the lateral fissure into three subgyri (the pars orbitalis [POr], pars triangularis [PT], and pars opercularis [Pop]), making it, more correctly, a gyral complex. The subgyri are differentiated cytoarchitectonically (Brodmann, 1909; Economo and Koskinas, 1925; Sarkissov et al., 1955; Petrides and Pandya, 1994, 2002, 2004; Amunts et al., 1999). Areas 44 and 45 (after Brodmann, 1909) are associated with the POp and PT, respectively. An area now referred to as 47/12 (Petrides and Pandya, 1994, 2002) is associated with the POr. However, there may be considerable variation among and within subjects in both the gross structure and the cytoarchitecture of the IFG, and the cytoarchitectonic borders do not consistently coincide with sulcal boundaries (Bailey and Bonin, 1951; Ebeling et al., 1989; Amunts et al., 1999; Tomaiuolo et al., 1999; Damasio, 2005).

Since Broca's original description of the effects of lesions of this area on speaking ability (1861; see translation by von Bonin, 1950), evidence for the IFG as a structure

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critical for speech and language function has come from many studies using a variety of experimental approaches including lesion/behavior (Mohr et al., 1978; Damasio and Geschwind, 1984), electrical stimulation functional mapping (Penfield and Roberts, 1959; Ojemann, 1979; Lesser et al., 1984; Ojemann et al., 1989), functional magnetic resonance imaging (fMRI; Wildgruber et al., 1996; Paulesu et al., 1997; Lazar et al., 2000), magnetoencephalography (MEG; Sasaki et al., 1995; Dhond et al., 2001), positron emission tomography (PET; Klein et al., 1997; Bookheimer et al., 2000; Caplan et al., 2000), and single-photon emission computed tomography (SPECT; Otsuki et al., 1998). These studies suggest that the IFG region is involved in numerous language-specific tasks including phonologic, semantic, and sentence- and discourse-level processing, as well as detection of the emotional content of speech (Gernsbacher and Kaschak, 2003; Martin, 2003). We hypothesized that in order for these different complex tasks to operate in a coordinated fashion during normal speech comprehension and production, the anatomically delineated subdivisions of the IFG believed to be involved in carrying out these tasks would be functionally interconnected.

Petrides and Pandya (2002) have shown by retrograde tracing methods in the rhesus monkey that the presumed homologues of areas 44, 45, and 47/12 are interconnected, suggesting that perhaps a similar pattern of connectivity exists in the human IFG. In order to understand the neural mechanisms involved in speech and language, however, it is essential to obtain as much information as possible on the underlying neural circuitry in humans. The modern anatomical tracer methods used so successfully to study corticocortical connections in non-human primates cannot be used in living human subjects. Electrical stimulation tract tracing has, however, proved to be an effective method to investigate functional connectivity between cortical areas in the living human brain (Rutecki et al., 1989; Wilson et al., 1990, 1991; Liegeois-Chauvel et al., 1991; Howard et al., 2000; Brugge et al., 2003, 2005; Matsumoto et al., 2004). The technique entails the delivery of an electrical impulse to one cortical site while one is recording electrical activity from distant cortical sites. The presence of a stimulus-evoked potential at a distant site is taken as prima facie evidence for a functional connection between the site of stimulation and the site(s) of the evoked response. We have recently identified a functional connection between the IFG and motor cortex in humans by using this method (Greenlee et al., 2004). In that same cohort of patients, we also noted that a stimulus applied to one subgyrus of the IFG could result in evoked activity in one or more of the other subgyri. Here we present the evidence for this functional connectivity within the IFG.

Abbreviations

AAR	anterior ascending ramus of lateral fissure
AHR	anterior horizontal ramus of lateral fissure
ASCS	anterior subcentral sulcus
CS	central sulcus
DS	diagonal sulcus
ESFM	electrical stimulation functional mapping
IFG	inferior frontal gyrus
IFS	inferior frontal sulcus
LF	lateral fissure
PCS	precentral sulcus
POp	pars opercularis
POr	pars orbitalis
PT	pars triangularis

MATERIALS AND METHODS

Subjects in this study (seven women and three men, average age 37 years [range, 20–53 years]) were patients undergoing surgical treatment of medically intractable temporal lobe epilepsy. For the five patients for whom we had histopathological results from resected temporal structures, diagnoses included no diagnostic abnormality, hippocampal cavernous angioma, oligodendroglioma, microdysgenesis, and focal dentate gyrus gliosis. The subjects represent a subset of patients from which data were also obtained for an earlier study (Greenlee et al., 2004). Patients were chosen for this study because they had multiple IFG sites stimulated with recording array coverage of IFG. All subjects gave written informed consent prior to participation. All protocols were approved by the University of Iowa Institutional Review Board. Patients did not incur additional medical risk by participating in this experimental protocol.

Extensive presurgical evaluation including neurological examinations, high-resolution brain imaging (MRI, PET, and SPECT), and neuropsychological testing revealed no evidence of frontal lobe damage or dysfunction in any subject. This evaluation confirming normal function, including language functions, of the brain region we investigated was particularly important given that cortical physiological and histopathological changes can be seen in patients with long-standing temporal lobe epilepsy. Preoperative sodium amobarbital (WADA) testing (Wada and Rasmussen, 1960) revealed that experiments were conducted on the left and language-dominant hemisphere of five subjects, on the left and language-predominant (if bilateral language representation was observed on the WADA exam) hemisphere of two subjects, and on the right and language-nondominant hemisphere of three subjects.

All experiments were conducted in the operating room during clinically necessary electrocorticography (ECoG) sessions. These sessions usually lasted about 30 minutes and were undertaken to clarify further the anatomical source of epileptic activity and thereby to guide the extent of resection. During experimental recording, 9 of the 10 subjects were awake and under local anesthesia. Electrical stimulation functional mapping (ESFM; charge-balanced pulses, 0.2-ms duration, 10–20 V, 50 Hz) was also undertaken in all subjects while they were awake by using standard neurosurgical techniques. Stimuli were applied to the cortical surface through a hand-held bipolar electrode and a Grass SD9 Grass: (West Warwick, RI) constant-voltage stimulator in an attempt to identify language-critical cortical sites on the IFG and to confirm the location of the orofacial motor cortex. The latter assists in identification of the precentral sulcus, which forms the posterior boundary of the IFG. Language-critical sites were identified in two of the five hemispheres determined previously by the WADA test to be speech and language dominant.

Electrical stimulation tract-tracing methods were the same as those described previously (Greenlee et al., 2004). A constant-voltage (Grass SD-9) or constant-current (Grass S12) stimulator was used to produce a single, 0.2-ms charge-balanced pulse, which was applied repeat-

edly at one IFG location while the resulting stimulus-evoked potentials were recorded from other IFG sites. Stimulation was carried out by using a custom-made bipolar stimulating electrode whose tips were silver balls approximately 2 mm in diameter and 2 mm apart. The stimulating electrode assembly was firmly fixed in position at each stimulus location. Responses evoked by IFG electrical stimulation were recorded by using a custom-manufactured 64-contact high-density electrode array. Each contact was 0.63 mm in diameter. Center-to-center contact separation was 3 mm. A platinum reference electrode was in contact with the galea near the vertex of the skull. In most cases pulse polarity was reversed for half the stimuli in an effort to minimize stimulus artifact. Potentials were amplified (5,000×, Grass Model 15 amplifiers) and filtered online (1 Hz to 6 kHz).

Responses obtained at each location to 30–50 stimuli were digitized online (sampling frequency 8 or 10 kHz, Hewlett Packard (Palo Alto, CA) VX-1 data acquisition system) and stored for off-line analysis. Records containing epileptic discharges or other artifacts were discarded prior to computation of the average waveform. Stimulation and recording sites were localized by using a 3D reconstruction of preoperative MRI images (Brainvox (Iowa City, IA); Damasio and Frank, 1992; Frank et al., 1997) or by using Analyze (Lenexa, KS) along with high-resolution intraoperative digital photographs. We estimate the error in localization of stimulus and recording locations to be 1–2 mm.

TABLE 1. Summary of Effects of Stimulating and Recording on the IFG[1]

Subject	Stimulation Site	Recording site POr	PT	POp
L79	POr			+
	PT			+
	POp			
R80	POr			+
	PT			+
	POp			
L81	POr			+
	PT			+
	POp			
R88	POr			+
	PT			+
	POp			+
L89	POr		+	+
	PT	−	+	
	POp			
L90	POr			
	PT		+	+
	POp			
L91	POr	+	+	+
	PT			+
	POp			+
L97	POr			
	PT		+	−
	POp			
L99	POr			−
	PT			+
	POp			
R102	POr			+
	PT			+
	POp			+

[1]Column 1: subject number with hemisphere studied (L, left; R, right). Column 2: IFG target stimulus sites. Columns 3–5; IFG target recording sites. Gray: area not contacted by recording grid. Black: area not stimulated. + evoked response at shown recording site to stimulation of site shown in column 2. −, no response at shown recording site to stimulation of site shown in column 2. In order to qualify as a +, the recording array had to contain at least two adjacent recording contacts that demonstrated a clearly visible, time-locked to the stimulus, difference in waveform amplitude compared with prestimulus background noise levels. For abbreviations, see list.

RESULTS

The tripartite structure of the IFG was evident in each of our 10 subjects, although this structure exhibited considerable intersubject variability, as described previously (Greenlee et al., 2004). In each subject we were able to identify the inferior frontal and precentral sulci along with the LF and its AAR and AHR. We also noted additional small sulci or dimples in some cases that tended to obscure the traditional tripartite IFG structure. For the purposes of the present study, we took the POp to be that cortex lying posterior to the AAR and anterior to either the anterior subcentral sulcus (Naidich et al., 1995), the precentral sulcus, or the motor cortex as defined by ESFM in cases in which the precentral sulcus was incomplete. The pars triangularis was taken to be the cortex between the AAR and the AHR. We referred to the POr as that cortex on the lateral surface of the brain ventral to the AHR.

Table 1 shows stimulation-recording pairings for each of the 10 subjects in our series and summarizes the results. Twenty-two different recording array placements were made in the 10 subjects, and 56 sites were stimulated. Recordings were obtained from the POp in all subjects studied, whereas in the PT data were obtained in four subjects, and in the POr there was only coverage in two subjects. In seven subjects we were able to record from more than one grid location, although in some cases this involved multiple recording sites on one IFG subgyrus. Typically, for a given grid placement, the recording array did not cover an entire subgyrus but extended over a small portion of an adjacent subgyrus. The bias in the distribution of recording sites toward the posterior aspect of the IFG reflects the nature and extent of the craniotomy performed during epilepsy surgery. It was this physical arrangement that provided the opportunity to record repeatedly from the POp in all subjects while electrically stimulating PT and POr. No obvious differences in data could be attributed to the hemisphere from which the data were obtained. In one subject we estimated the stimulus threshold to be between 5 and 7.5 V. Time constraints prevented us from systematically determining threshold or studying the effects of changing stimulus strength.

The response to an effective electrical stimulus was typically a cluster of polyphasic evoked potentials, which we refer to as a *response field*. Within a response field, the amplitude of the evoked response was usually highest at one, or perhaps a few, neighboring recording locations, and then diminished systematically with distance from these sites. Figure 1 illustrates four response fields (Fig. 1C–F) obtained from the same area of the POp when electrical stimuli were applied to each of four different sites (Fig. 1A,B) located on the POr (site 1), on the PT (sites 2,3), and anteriorly on the POp (site 4). The extent and position of the response field on the POp depended on the locus of stimulation. Stimulating sites 1 (Fig. 1C, POr) and 3 (Fig. 1E, anterior PT) resulted in response fields that overlapped substantially; they both extended dorsoventrally along and on either side of the DS.

These data suggest that our electrical stimuli activated circuits in the POr and PT that converge on the POp. Evoked potentials in both response fields exhibited phase reversal in the vicinity of the DS and the AAR, suggesting that the dipole source of some of this activity may have been within one or both of these sulci. Stimulation of site 2 (Fig. 1D, posterior PT) resulted in a more restricted response field that overlapped ventrally the response

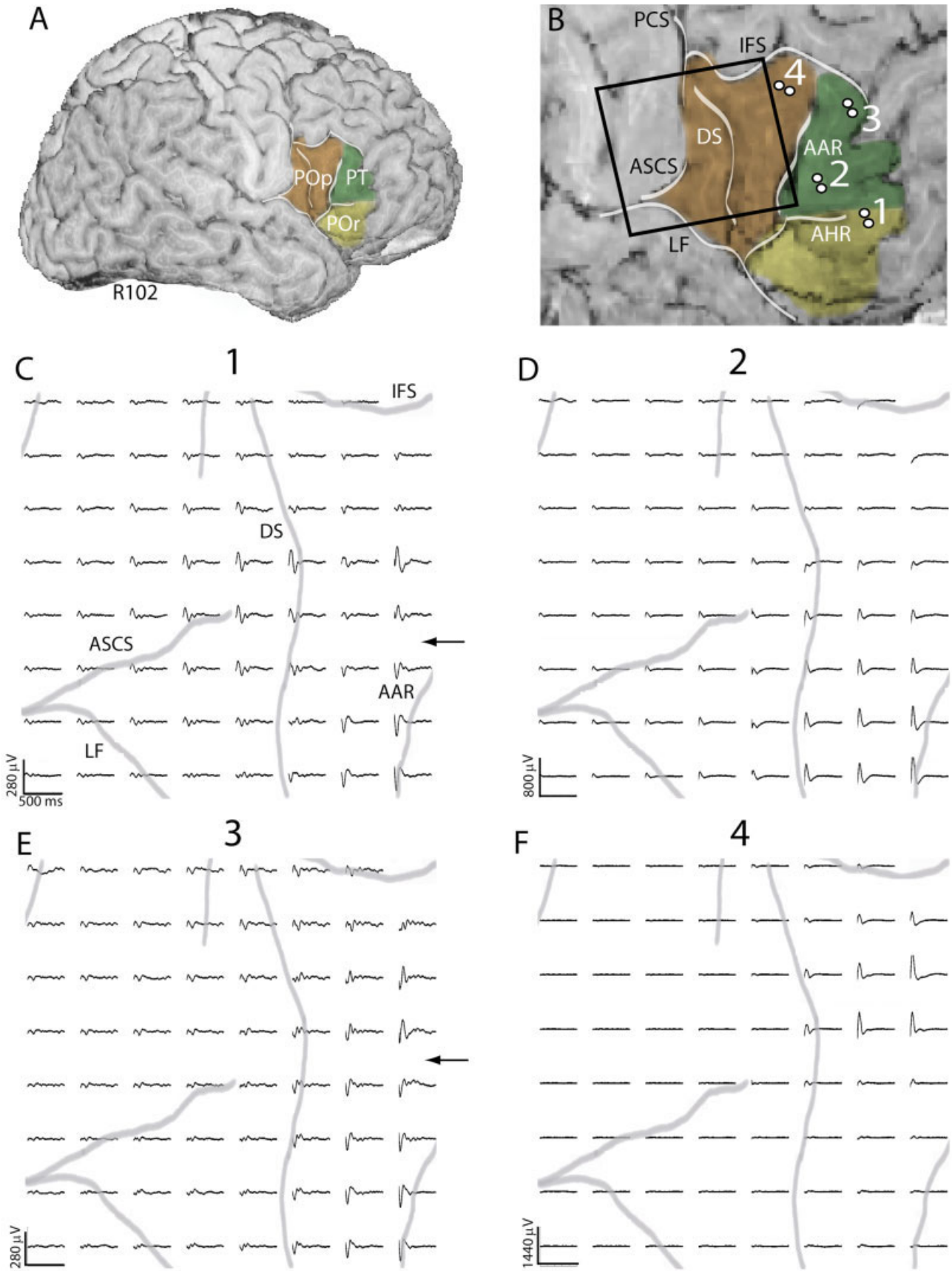

Fig. 1. **A:** Lateral MRI surface rendering from subject R102 with IFG subgyri labeled and sulci traced. In this and all subsequent figures colors denote the POr (yellow), the PT (green), and the POp (orange) **B:** Expanded view of the IFG with major sulci (white lines) labeled, four sites of stimulation (paired open circles), and position of the recording array (black box, 25-mm square) indicated. **C–F:** Response fields resulting from stimulation at each of the numbered sites. The arrows indicate an area of phase reversal seen in the evoked waveform. Prominent sulci are shown as gray lines, and named sulci are labeled. In this and all subsequent figures positive voltages are plotted downward. For abbreviations, see list.

fields resulting from stimulation of sites 1 (POr) and 3 (PT), but it exhibited no phase reversal. The response field resulting from stimulation of site 4 (Fig. 1F, anterior POp) was also highly restricted, but it overlapped the dorsal portion of response fields resulting from stimulation of sites 1 and 3. On the other hand, input to the POp from disparate stimulus sites 2 (posterior PT) and 4 (anterior POp) remained relatively segregated.

Response fields shown in Figure 2 (C,E,G) extend our findings to observed inputs to the POp from the POr. In this experiment, recordings were made from the grid covering the caudal aspect of the POp and a portion of the precentral gyrus, whereas a stimulus was applied to one site on the POr and to two on the PT (Fig. 2A,B). Below each response field (Fig. 2D,F,H) is a family of evoked waveforms recorded from a row of electrodes on the anterior border of the grid (outlined by rectangles in Fig. 2C,E,G and by a linear array of closed circles in Fig. 2B). Dashed lines are drawn through two large deflections, the latencies of which are given below each column. In this case, as in the case illustrated in Figure 1, different sites within the PT send convergent input to the POp. We also see that the response fields generated by stimulation of the POr overlap those obtained by PT stimulation, suggesting that the POr may be considered another component of convergent input. The large positive deflection (latency 30 ms) recorded from the three dorsal grid contacts when the POr was stimulated (Fig. 2D) exhibited a phase reversal at more ventral locations near the DS (arrow), suggesting again that the source dipoles generating these evoked responses lay within the sulcus.

A relatively abrupt change in the waveform, although more complex and not a clear phase reversal, was seen in the same vicinity when each of the two PT sites was stimulated (Fig. 2F,H). We also note that although the three stimulus sites appear to send convergent input to the POp, the shapes of the waveforms resulting from stimulation of each the three sites differed considerably, suggesting that the neural circuitry responsible for generating each of these waveforms differs as well.

The pars triangularis, like the POp, also receives convergent input, from the POr and from the nearby PT. In another subject, with the grid held at one location, a response field was recorded on the PT to stimulation of the POr. (Fig. 3B,C, Experiment 1). The response field consisted of complex evoked potentials that aggregated in the anteroventral PT (dashed oval). The grid was then moved more anteriorly (Fig. 3F,G, Experiment 2), and the stimulus was applied to a site on the posterior PT. The resulting response field was nearly coextensive with that obtained in Experiment 1, suggesting that there was convergent input to the anteroventral PT from the two stimulus sites. Comparing waveforms, we see that those evoked by stimulation of the POr (Fig. 3D,E) exhibited several prominent negative deflections, whereas stimulation of the posterior PT (Fig. 3H,I) resulted in a waveform that consisted of one major negative peak followed by a shallow positive deflection and a broad negative wave.

The data presented so far illustrate what appear to represent widespread functional connections between and within the anatomically defined subgyri of the IFG. The degree to which the response fields overlap or remain segregated may be taken to reflect the degree of divergence and convergence of these connections.

Figure 4 illustrates the results of two experiments carried out on the same subject that were designed to examine further the topography of IFG projections not explicitly shown in previous figures. In Experiment 1, the recording array covered almost all of the POp along with a small portion of the precentral gyrus. The response field recorded following stimulation of the POr (Fig. 4B, small paired open circles) was distributed dorsoventrally along the AAR (Fig. 4C). Examination of the waveforms suggests a phase reversal near the AAR (Fig. 4C–E), although the loss of data at one critical recording site makes this difficult to discern. In Experiment 2, the recording array was placed over the posterior portion of the POp as well as the pre- and postcentral gyri (Fig. 4G). The electrical stimulus was applied on or very near the dorsalmost area of the POp (Fig. 4G, open paired circles) from which response fields were obtained to POr stimulation. This site was also identified as a language-critical area (subjects were unable to name visually presented objects during ESFM stimulation) on the anterior and superiormost region of the POp. The response field resulting from this stimulus was recorded on the posterior superior area of the POp (Fig. 4H). This same cortical region was seen to be activated by POr stimulation (Experiment 1, Fig. 4C,F). The activation of the posterior superior area of the POp is similar to that shown in Figures 1 and 2, although on the opposite (left) cerebral hemisphere.

The potentials evoked by electrical stimulation were generally triphasic in form, with an early small deflection followed by a large negative wave and a second large but broader positive wave (Figs. 1C–F, 3G–I, 4C,D). In some instances, a second large negative deflection was seen (Figs. 3C–E, 4H–J). The latencies of the major deflections varied both within a response field and between response fields. The earliest deflection was often obscured by stimulus artifact. For those 18 evoked potentials in seven subjects in whom the earliest wave was identifiable, we were able to measure the latency to its onset. The mean onset latency for this set of evoked potentials was 4.9 ms (range, 2.8–10 ms).

DISCUSSION

Our findings with respect to interconnections within and between subdivisions of the IFG were obtained through electrical stimulation tract tracing in human neurosurgical patients, an approach used successfully in earlier studies to reveal connectivity patterns in vivo in the human brain (Rutecki et al., 1989; Wilson et al., 1990, 1991; Liegeois-Chauvel et al., 1991; Howard et al., 2000; Brugge et al., 2003, 2005; Greenlee et al., 2004; Matsumoto et al., 2004). Although data obtained by this method gave no direct information on the cellular origins, anatomical trajectories, or terminal arbors associated with IFG-IFG pathways, they did provide evidence for interconnections both within and between the subdivisions of the IFG, showed that the spatial distributions exhibited were consistent with both divergent and convergent projections, and, from latency measurements of evoked waveforms, allowed us to estimate transmission times from the site of stimulation to the loci of evoked responses.

The nature and extent of the craniotomy performed for epilepsy surgery in our subjects resulted in the recording grid most often being placed mainly on the POp. In seven of the hemispheres, we recorded response fields on the

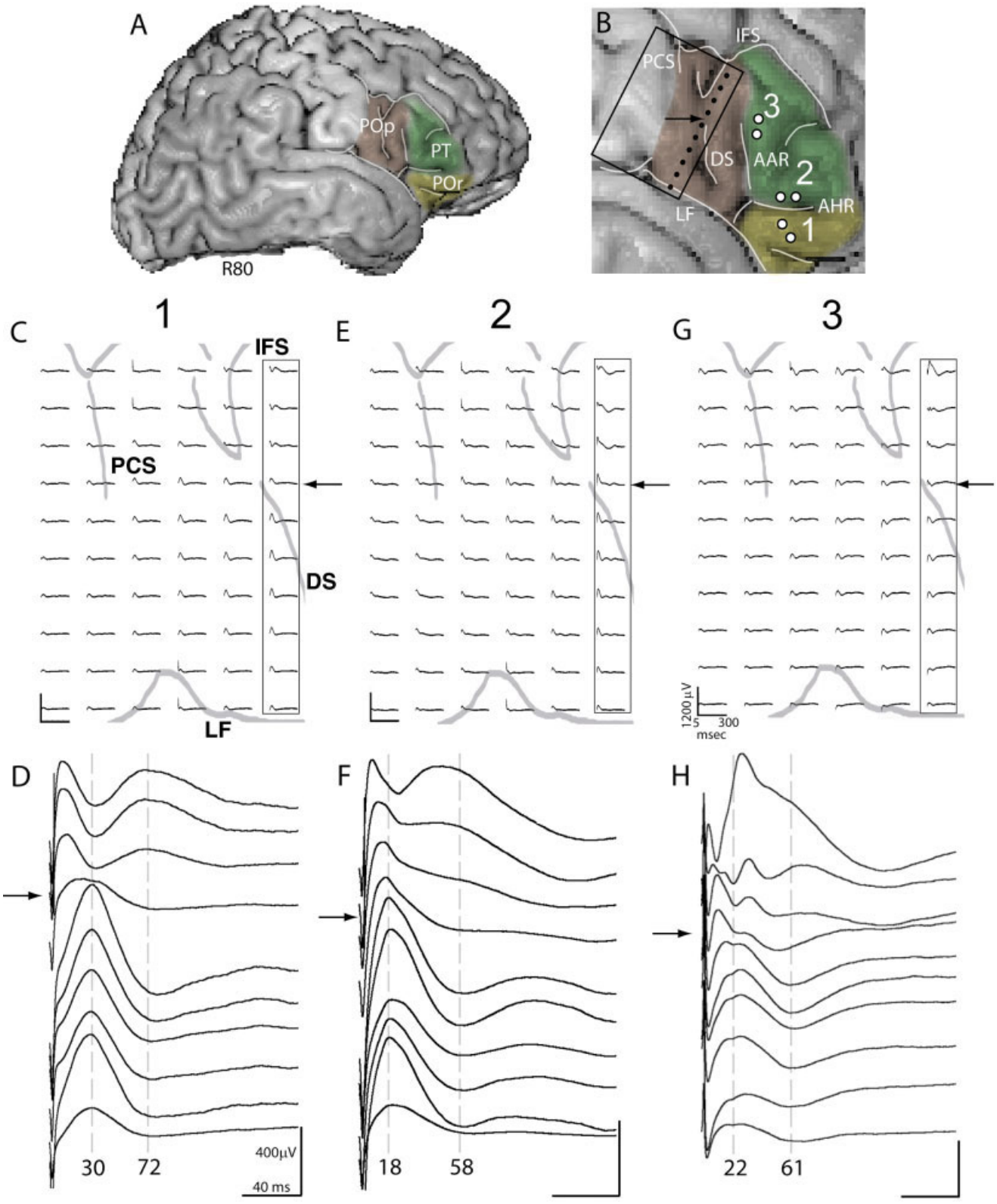

Fig. 2. **A:** Lateral MRI surface rendering of subject R80 with IFG subgyri labeled and sulci traced. **B:** Expanded view of the IFG with major sulci (white lines), three sites of stimulation (paired open circles), and position of the recording array (black box, 22 &time;s 31 mm) indicated. The filled black circles indicate the position of the anteriormost 10 recording contacts within the grid. **C,E,G:** Response fields resulting from stimulation of each of the numbered sites shown in B. The thin black rectangle indicates the anteriormost contacts shown in B. Sulci are shown as gray lines. **D,F,H:** Enlarged and rescaled evoked waveforms obtained from the anteriormost row of contacts to stimulation of each of the sites shown in B. Time and amplitude scales are the same for all. Arrows indicate an area of marked transitions in the evoked waveform. Dashed lines, labeled in msec, point to prominent deflections in the evoked waveforms. For abbreviations, see list.

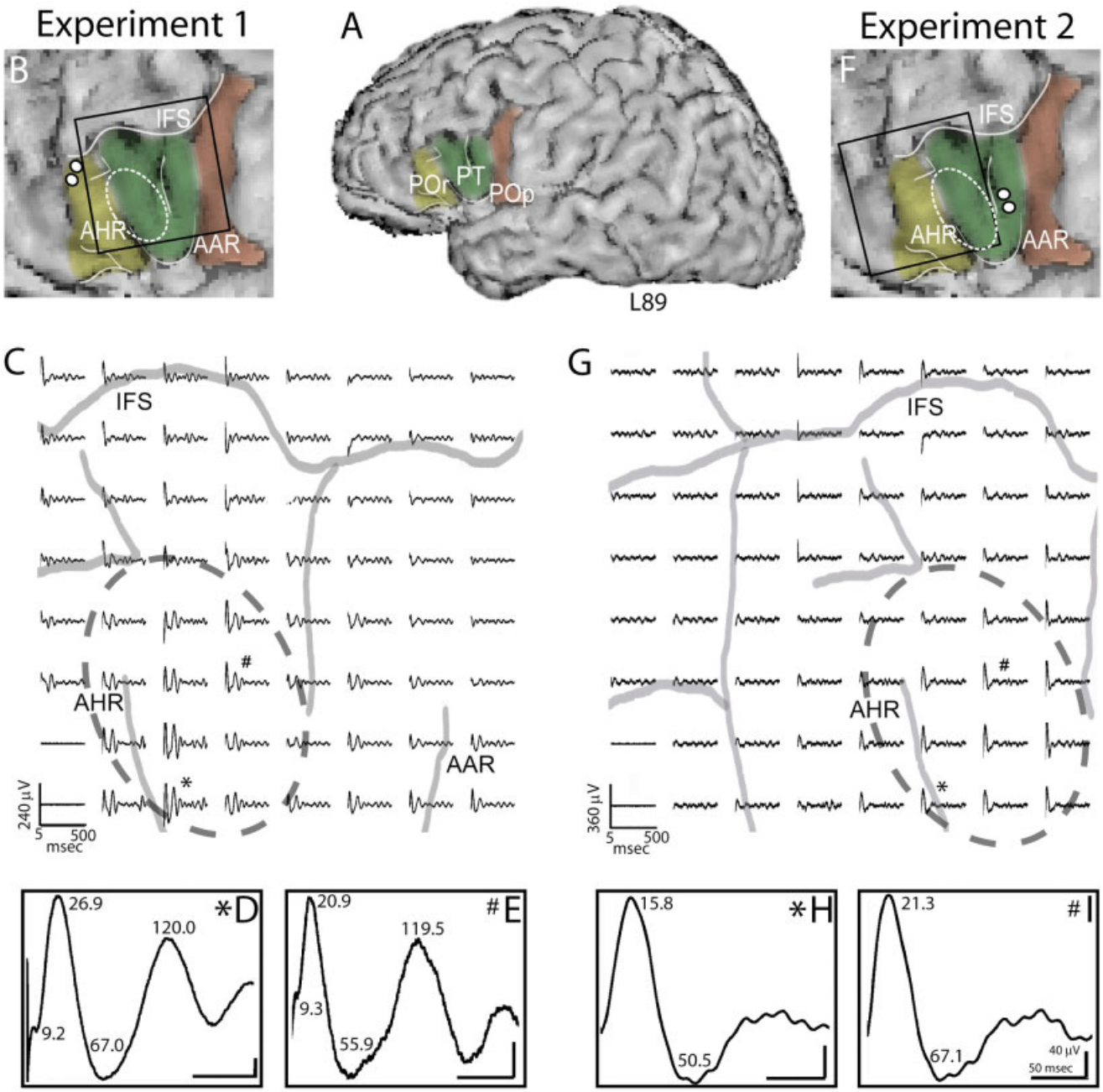

Fig. 3. **A:** Lateral MRI surface rendering of subject L89 with IFG subgyri labeled and sulci traced. Results of two experiments (B–E) and (F–I) are shown. **B,F:** Expanded view of the IFG with major sulci (white lines), sites of stimulation (paired open circles), and position of recording array (black box, 25-mm square) indicated. **C,G:** Response fields (dashed ovals) resulting from electrical stimulation of sites shown in B and F, respectively. Local sulci are depicted as gray lines. **D–I:** Enlarged and rescaled evoked waveforms from the two sites, denoted by * and #, within each of the response fields. In this and the subsequent figure, peak latency is shown in msec. For abbreviations, see list.Scale bar = 50 msec and 40 µV for D–J.

POp as the result of stimulating the PT or POr. Four were left hemisphere, language-dominant cases as determined by WADA testing. These data provided the most compelling evidence that one or more pathways exist over which the PT and POr of either cerebral hemisphere may exert an influence on the POp. Diffusion tensor magnetic resonance imaging (DT-MRI) has been shown to be capable of identifying noninvasively specific white matter tracts in the human brain in vivo, including corticocortical pathways thought to be involved in hearing, speech, and language (Parker et al. 2002).

Combining this MRI approach with intraoperative ESFM, Henry et al. (2004) were able to identify a connection between a site in Broca's area, stimulation of which

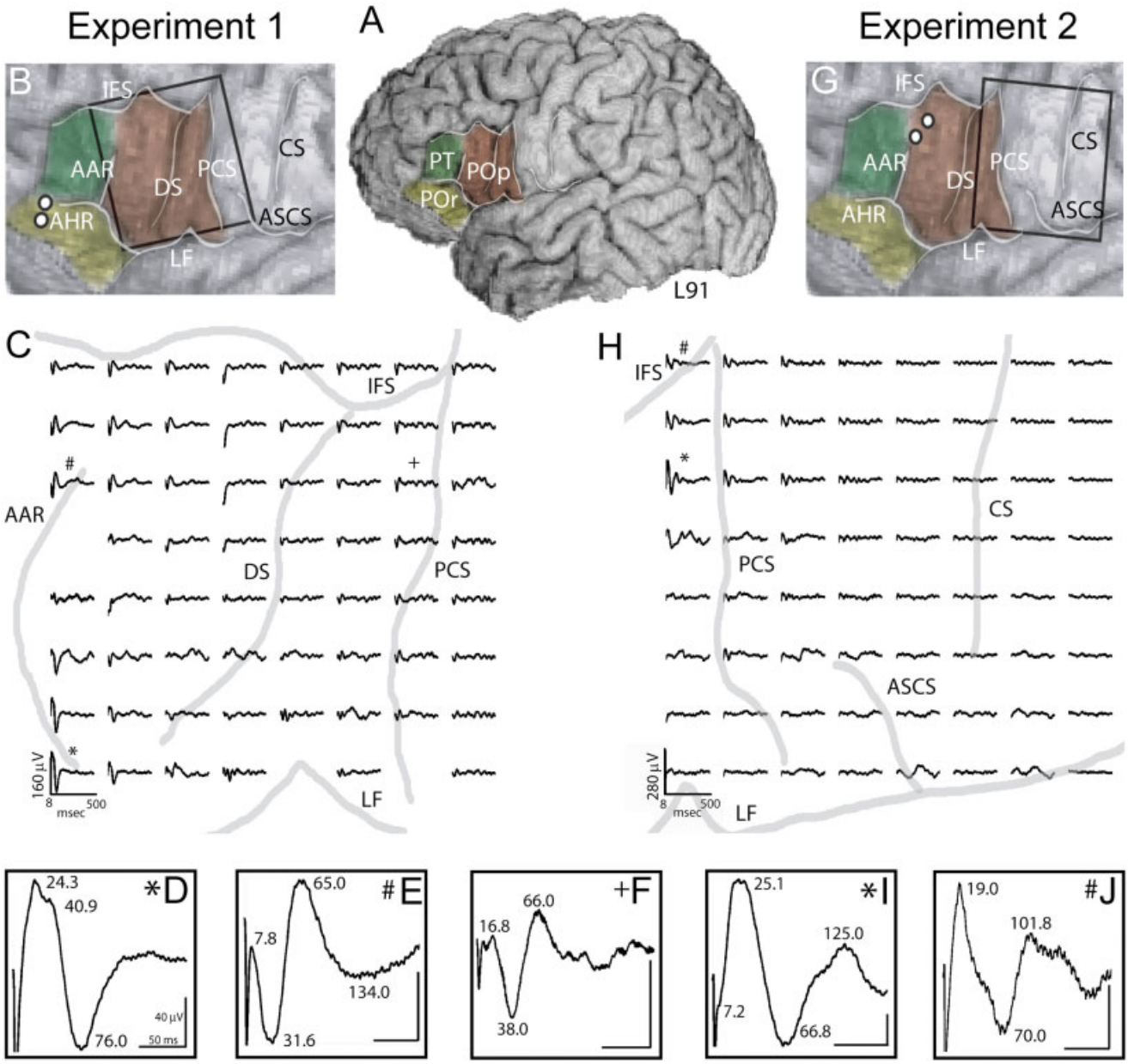

Fig. 4. **A:** Lateral MRI surface rendering of subject L91 with IFG subgyri labeled and sulci traced. **B,G:** Expanded view of the IFG with major sulci (white lines), sites of stimulation (paired open circles), and position of the recording array (black box, 25-mm square) indicated. **C,H:** Response fields resulting from electrical stimulation of sites shown in B and G, respectively. Gray lines denote prominent sulci. **D–J:** Enlarged and rescaled evoked waveforms from sites within each of the response fields denoted by *, #, and +. For abbreviations, see list. Scale bar = 50 msec and 40 µV for D–F,I,J.

resulted in anomia with another region in the IFG (which they interpreted as being areas 44 and 45, respectively). Our finding of functional connectivity between the POp (area 44) and PT (area 45) agrees with this anatomical finding. The presumed homologues of Brodmann's areas 44 and 45 in the rhesus monkey have been found on caudal and rostral banks, respectively, of the inferior limb of the arcuate sulcus; these fields adjoin the more ventrally located area 47/12 (Petrides and Pandya, 1994, 1999, 2002, Petrides et al., 2005). Petrides and Pandya (2002) have reported that areas 44 and 45 are reciprocally connected with area 47/12, which agrees both with our findings and with those of Henry et al. (2004).

We were successful in recording from the PT in only four subjects. In two of these we obtained a response field following stimulation of the POr. Because of the surgical exposure in these patients, however, we report only a single case of successful recording on the POr.

In all four cases in which the grid was in contact with the PT, stimulation of one site on the PT resulted in a response field on a distant area on the same subgyrus. A similar finding was made with respect to the POp in three

other subjects, and to the POr in a single case. These data suggest that intrinsic functional connections exist within each of the subgyri. Although the anatomical methods used so successfully in laboratory animals to trace cortical pathways in vivo cannot be used in human subjects, lipophilic fluorescent dyes placed in fixed postmortem human cortex have been shown to fill axons for distances of millimeters (Mufson et al., 1990; Galuske et al., 1999, Sparks et al., 2000; Swift et al., 2005). This approach is generally not suited to studies in which many of the possible pathways linking subdivisions of the IFG would greatly exceed these distances, but it may prove useful in the future for tracing anatomically shorter connections within a subgyrus that our electrophysiological data suggest exist.

An electrical stimulus applied at a single cortical site resulted in evoked responses at multiple distant sites on the same or different subgyrus. These active recording sites were contiguous, forming what we refer to as a response field. These largely circumscribed response fields typically exhibited a region within them in which the amplitudes of the evoked responses were markedly increased compared with those recorded from the surrounding contacts. Our interpretation of the response field is that it reflects the spatial extent of a divergent projection arising from a neuronal pool activated by the distant electrical stimulus. Time did not allow us to determine the extent to which the size and shape of a response field may have been dependent on the intensity of the stimulus.

Response fields arising from stimulation of different IFG sites often overlapped considerably, indicating that the inputs giving rise to the response fields converged upon the overlapping cortical area from the respective neuronal pools activated by the distant stimulation. Although the spatial distribution of input from two distant sites may have shared a common cortical target, the typically polyphasic waveforms that made up the overlapping response fields could differ substantially in their morphology, which suggests that input from each of the distant sites is processed in a different way and that these inputs may interact in complex ways during normal physiologic activation.

Typically, stimulation of one site on the IFG evoked waveforms consisting of a series of positive and negative deflections, the earliest of which may be interpreted as a sign of the invasion of the afferent volley of impulses resulting from distant stimulation. In many cases the stimulus artifact affected the first 10 ms or so of recording, thereby obscuring what may have been an early evoked potential. In those cases in which this did not occur, we were able to measure the onset and peak latencies of the small initial deflections. These ranged from 2.8 to 10 msec (mean 4.9). We estimate, from examining the MRIs of each of the 10 subjects, that the distances between stimulus and recording sites in our experiments ranged from 1 to 5 cm. Bishop and Smith (1964) reported that axons in the human frontal lobe range in diameter from 1 to 4 μm.

Using these values, and assuming that the earliest deflection reflects a direct corticocortical connection, we estimate that the conduction velocity for axons of this pathway ranges from 1.3 to 18.0 m/sec. This range of values is consistent with corticocortical conduction velocities observed in experimental animals (Swadlow et al., 1978; Swadlow, 1994) and with those we reported previously in a study of IFG- motor cortex connections (Greenlee et al., 2004). Interpretation of the later deflections in our evoked responses is more tentative. These deflections, with peak latencies greater than about 15 ms, may reflect intrinsic activity aroused by incoming afferent volleys and/or by activity arriving over pathways having multiple synaptic interruptions in either another cortical field, a subcortical site, or both. These are plausible explanations considering the widespread afferent and efferent connections of the IFG (human: Parker et al., 2002; monkey: Deacon, 1992; Kurata, 1994; Romanski et al., 1999; Petrides and Pandya, 2002; Romanski and Goldman-Rakic, 2002).

The functional significance of the connectivity we have demonstrated within the IFG remains unknown. Our focus thus far has been on the role of the IFG in auditory and language processing. However, interconnections within the IFG may be part of a network subserving a far wider range of functions including motor control (Rizzolatti and Arbib, 1998; Binkofski et al., 2000; Heiser et al., 2003) and working memory (Braver et al., 1997; Binkofski et al., 2000; Campbell et al., 2001; Hsieh et al., 2001).

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LITERATURE CITED

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