Cerebral Cortex Advance Access published October 5, 2007

Cerebral Cortex
doi:10.1093/cercor/bhm169

A Discrete Area within the Left Dorsolateral Prefrontal Cortex Involved in Visual–Verbal Incongruence Judgment

Monique Plaza[1], Peggy Gatignol[1], Henri Cohen[1], Brigitte Berger[1] and Hugues Duffau[1,2]

[1]Laboratoire de Psychologie et de Neurosciences Cognitives, FRE 2987 (CNRS/Université de Paris V René Descartes), Institut de Psychologie, 71 avenue Edouard Vaillant, 92774 Boulogne Billancourt, France and [2]Département de Neurochirurgie, Centre Hospitalier Universitaire Gui de Chauliac, Montpellier, France

The role of the frontal lobe in cross-modal visual–auditory processing has been documented in experiments using incongruent/congruent paradigms. In this study, 4 patients with left frontal World Health Organization Grade II glioma were assessed during pre-, intra-, and postoperative sessions with picture-naming and verbal–visual task requiring judgment of congruence between pictures and words. During awake brain surgery, the naming and cross-modal tasks were coupled with electrical stimulation inactivating restricted specific regions. For all patients, focal brain stimulation in the dorsolateral prefrontal cortex elicited picture–word matching disturbances but no naming impairment, and the elicited errors exclusively appeared in incongruent and not congruent conditions. The dissociation observed between correct picture naming and disturbed cross-modal judgment shows that electrical stimulation of a discrete cortical area within the left dorsolateral prefrontal cortex can inhibit the simultaneous processing of visual–verbal information without disturbing larger networks involved in the naming process.

Keywords: electrical brain stimulation, judgment, left dorsolateral prefrontal cortex, phonology, visual–verbal incongruence

Introduction

Information from different modalities is integrated by the brain producing accurate and meaningful representation unobtainable from modalities taken in isolation (Molhom et al. 2004; Booth et al. 2005; Ross et al., 2007). The neurological literature on cross-modal visual–verbal processing has made it clear that large brain networks, notably in parietal, occipital, and temporal regions, contribute to the multimodal object representations (Calvert 2001; Molhom et al. 2006; Taylor et al. 2006; Saint-Amour et al. 2007).

The role of the frontal lobe in cross-modal visual–auditory processing has been documented in experiments using incongruent/congruent paradigms. Evoked related potentials (ERP) studies showed that negative components were elicited in the prefrontal cortex for incongruent pairs in experiments when gender information between male- and female-voiced syllables was matched with women and men photographs (Wang et al. 2002) and when phonologically or semantically incongruent words were paired with visual scenes (D'Arcy et al. 2004). Congruent cross-modal stimuli specifically enhanced behavioral performance, whereas incongruent stimulus pairs resulted in behavioral decrements (Laurienti et al. 2004). But the role of prefrontal areas in congruence judgment is less clear.

Functional magnetic resonance imaging (fMRI), repetitive transcranial magnetic stimulation (rTMS), and ERP studies showed that the prefrontal cortex, notably the dorsolateral prefrontal cortex (DLPFC), contains a general mechanism for integrating perceptual information, independent of stimulus and response modalities, and for controlling various behaviors and decisions (Sirigu et al. 1995; Koechlin et al. 2000; Krawczyk 2002; Wood and Grafman 2003; Heekeren et al. 2004; Dudukovic and Wagner 2007; Fecteau et al. 2007; Herwig et al. 2007).The DLPFC is involved in the semantic processing of idiomatic—and not literal—sentences (Rizzo et al. 2007) and the maintenance of verbal working memory (Osaka et al. 2007).

In this study, we implemented a visual–verbal judgment task during electrical brain stimulation in 4 patients with left frontal World Health Organization (WHO) Grade II glioma in order to determine whether the left frontal area is specifically involved in cross-modal visual–verbal integration. Considering the wide role of prefrontal areas, we contrasted picture-naming and picture–word matching tasks and focused on "phonological" and "semantic" matching in "congruent" versus "incongruent" conditions. Our observations were based on intraoperative assessment during cortical stimulation in awake patients. We hypothesized that the stimulation of some discrete prefrontal areas could induce cross-modal disturbances, notably in the incongruent condition, without generating any naming impairment. As the role of prefrontal areas in congruence judgment is less clear, direct electrical mapping should be useful for addressing this question.

Materials and Methods

Participants

Four French right-handed adults were operated while awake on a left frontal WHO Grade II glioma using electrical language mapping. Patients were 2 women (IJ, 33 years and CC, 28 years) and 2 men (FV, 29 years and PR, 36 years), all with tumors revealed by seizures. Figure 1 shows the precise location of each tumor within the frontal lobe.

All patients had normal preoperative neurological and neuropsychological examinations. In particular, preoperative performances on the "Boston Diagnostic Aphasia Examination" (Goodglass and Kaplan 1983) as well as on the picture-naming test "DO 80" (Metz-Lutz et al. 1991) were normal. The 4 subjects displayed neither auditory nor phonological impairment in language reception or production (see Table 1).

Surgical Procedure

Patients were placed in a lateral position on their right side. Intraoperative mapping was performed under local anesthesia using the technique of direct electrical stimulation already described by the authors (Duffau 2005; Thiebaut de Schotten et al. 2005). Briefly, a bipolar electrode with 5-mm spaced tips delivering a biphasic current nondeleterious for the nervous system (pulse frequency of 60 Hz, single pulse phase duration of 1 ms, amplitude from 2 to 6 mA) was placed on the patient's brain while awake. The stimulation began 0.5 ms before the presentation of the cross-modal stimuli and lasted 4 s.

Sensory-motor and language functions were assessed. Patients were first asked to count (repetitively from 1 to 10) in order to identify the

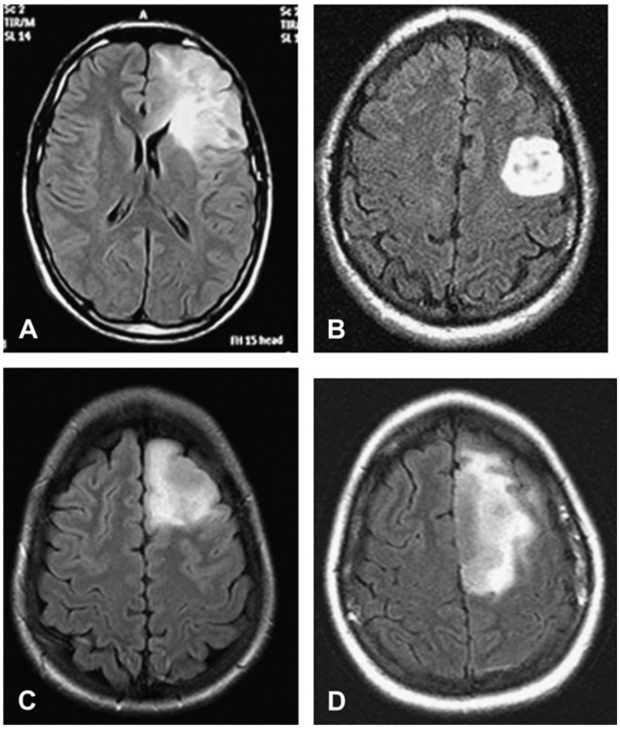

Figure 1. Preoperative axial fluid attenuation inversion recovery-weighted MRIs showing tumor locations. (*A*) For patient FV, image reveals a left precentral glioma involving the middle and inferior frontal gyri. (*B*) Patient PR has a left precentral glioma involving the middle frontal gyrus. (*C*, *D*) Images show, for patients IJ and CC, respectively, a left mesial precentral glioma involving the superior frontal gyrus at the level of the supplementary motor area.

areas essential for speech production, namely those with complete anarthria when stimulated. Second, a picture-naming test (DO 80) consisting of 80 black and white drawings of objects was used to detect anomia and naming impairment—frequent symptoms in the aphasic syndromes. In this test, the required answer is short and thus easily produced during brain stimulation. This is why picture naming is the "Gold Standard" language task in intraoperative electrical mapping (Gatignol et al. 2004).

The patient, the speech therapist, and the experimenter were all blind as to when the brain was stimulated. Each site was tested at least 3 times, 3 trials being enough to establish whether a cortical site is essential for a particular cognitive function (Ojemann et al. 1989). To avoid seizures, the same cortical site was never stimulated twice in a row. To ensure successful tumor removal while sparing functional areas, the limits of the resections were progressively set so as to preserve functional pathways in the immediate vicinity of the surgical cavity. Such a procedure minimizes residual morbidity while enhancing resection quality (Duffau 2005).

Cross-Modal Tasks

The tasks were presented on a portable computer, including pictures taken from the naming test (DO 80) and words spoken by a woman. Visual and verbal stimuli were presented simultaneous. Pictures were presented for 4 s with a 250-ms interstimuli interval. The design included 2 conditions. In the congruent condition, the visual and verbal stimuli referred to the same item. In the incongruent condition, the visual and verbal stimuli differed either semantically (e.g., "sofa" matched with a picture of an armchair) or phonetically (e.g., "groix" [grwa] matched with a picture of "croix" [krwa], i.e., a cross). Incongruence was thus expressed in terms of incompatible phonological (phonemic feature) or semantic (meaning word form) expectations.

Task A, used in the pre- and postoperative assessments, involved 58 paired visual–verbal stimuli randomly presented in order to control for stimulus order effects. There were 30 congruent, 14 phonologically incongruent, and 14 semantically incongruent pairs. Semantically, all erroneous items belonged to the same conceptual category as the target (e.g., mammoth/elephant, sofa/armchair). The phonological errors involved consonant or vocalic substitutions in initial or medial position (e.g., t/k, p/f, p/b, and o/u). The phonologically mismatched pairs included 14 real or pseudowords differing by one phoneme only (e.g., "balais/palais": [pale/bale]; "étoile/itoile" [etwal/itwal]).

Task B, used in the intraoperative assessment, included 50 visual–verbal pairs of stimuli taken from Task A. Task B was shorter than Task A due to surgical constraints. There were 30 congruent, 10 phonologically incongruent, and 10 semantically incongruent pairs presented in a fixed order. The operating surgeon knew which stimuli were congruent or incongruent during the electrical stimulation of brain areas, so as to exactly administer the same number of stimulations in each condition. Only sites in which electrical stimulation had induced neither counting nor naming disturbances were tested with the cross-modal Task B. Stimulation begun just before stimulus presentation. During the first experiment (with patient FV), the surgeon did not know a priori that prefrontal sites could be "eloquent" for cross-modal judgment. He only knew that he must avoid (and preserve) the sites in which stimulation induced naming disturbances, so the experimenters began to present cross-modal task when stimulation did not produce anymore naming errors in the prefrontal cortex. Each of the "naming silent" prefrontal cortical sites was systematically tested 3 times during the cross-modal task in each condition (congruent, phonologically incongruent, and semantically incongruent pairs), that is, 9 times per site. Moreover, as patients performed cross-modal task with and without stimulation, a baseline performance could be established during surgery, determining stimulation-specific effects. Thus, 3 tasks allowed to determine the specific cross-modal judgment performance during surgery: the naming test, the cross-modal assessment made the day before surgery, and the baseline performance without stimulation.

Subjects were asked to look at the computer screen and report (yes/no response) whether the visual and verbal stimuli were congruent. The subjects heard the verbal stimuli through an amplifier, adapted to the acoustics of the surgical theater. They were instructed to respond as rapidly and accurately as possible. Verbal responses were recorded, and no feedback was given. In order to delineate the resection area, the surgeon was informed of the items on which the patient committed errors during surgery and not the day before.

Data analyses were based on comparisons between pre-, intra-, and postoperative assessments of cross-modal processing (Table 2). For each patient, Task A items with a wrong answer during pre- and postoperative sessions were excluded. Only errors committed by each patient during the intraoperative assessment on Task B, and correlated with the focal electrical stimulation, were considered. We reported in Table 3 all patient responses, with and without stimulation, and calculated by successive *t*-tests whether differences were significant between phonological and semantic, congruent and incongruent items.

Results

Pre-, Intra-, and Postoperative Visual–Verbal Skills in the 4 Patients

Preoperative Results

Performance was globally good for all subjects on Task A (2 or 3 errors, e.g., overall correct score >95%), and there were no errors with congruent items.

Intraoperative Results

All items processed without stimulation, as well as congruent items of Task B during the 12 electrical stimulations, were correctly performed.

Performance was correct on all congruent items of Task B during the 12 electrical stimulations. In contrast, during the 24 electrical stimulations related to the incongruent pairs, the

Table 1
Results of Boston Diagnosis Apnasia Examination (BDAE) in the preoperative assessment

Domain	Subtest	FV	PR	IJ	CC
Auditory comprehension	Picture pointing	72/72	72/72	72/72	72/72
	Body parts	20/20	20/20	16/20	16/20
	Instructions	14/15	14/15	14/15	15/15
	Reasoning	10/12	10/12	12/12	7/12
Fluency	Articulation	7/7	7/7	7/7	7/7
	Sentence length	7/7	7/7	7/7	7/7
	Sequence repetition	14/14	13/14	14/14	13/14
Automatic speech	Series	9/9	9/9	9/9	9/9
	Recitation	2/2	2/2	2/2	2/2
Repetition	Words	10/10	10/10	9.5/10	10/10
	Concrete sentences	8/8	8/8	8/8	7/8
	Abstract sentences	6/8	8/8	8/8	8/8
Oral reading	Words	30/30	30/30	30/30	30/30
	Sentences	10/10	10/10	10/10	10/10
Naming	Definition	30/30	30/30	30/30	30/30
	Pictures	105/105	105/105	105/105	103/105
	Body parts	30/30	30/30	30/30	29/30
Aphasic troubles	Phonemic troubles	2	0	0	0
	Jargon	0	0	0	0
Written comprehension	Letters discrimination	10/10	10/10	10/10	10/10
	Verbal recitation	8/8	8/8	8/8	8/8
	Spelled words	8/8	6/8	8/8	8/8
	Words/pictures matching	10/10	10/10	10/10	10/10
	Text reading	10/10	10/10	10/10	10/10
Spelling	Writing	3/3	3/3	3/3	3/3
	Automatic spelling	46/46	46/46	46/46	46/46
	Dictation	15/15	15/15	15/15	15/15
	Written naming	10/10	9/10	10/10	10/10
	Graphic evocation	10/10	8/10	10/10	10/10
	Sentences dictation	12/12	9/12	12/12	12/12
	Description	4/4	4/4	4/4	4/4
Music	Song	2/2	2/2	2/2	2/2
	Rhythm	2/2	2/2	2/2	2/2

patients produced 17 specific cross-modal judgment errors and no congruence judgment errors. The phonological errors were related to consonant and vocalic phonemes such as t/k, p/f, b/p, s/z, and o/u. The 3 semantic errors were produced with the word pairs "fraise/cerise" (strawberry/cherry; produced twice) and "mammouth/éléphant" (mammoth/elephant).

The intraoperative results show that, only under electrical stimulation of the DLPFC, the patients committed 17/24 incongruence judgment errors (3 semantic and 14 phonological) versus 0/12 congruence judgment error. In all patients, none of the other prefrontal site generated cross-modal errors when stimulated. For 2 patients (FV and CC), subcortical stimulation immediately under the DLPFC generated cross-modal incongruence judgment errors. The *t*-tests show that the differences between phonological and semantic, congruent and incongruent items were statistically significant ($P < 0.01$).

Postoperative Results

Six days after the surgical procedure, the 4 patients performed Task A with near-perfect accuracy: in all, 5 phonological and 2 semantic errors were committed, unrelated to those produced during the visual–verbal mapping procedure. It is worth noting that the 4 patients completely recovered from the transitory cognitive and linguistic impairments displayed after intervention. Several days after the surgical intervention, the 4 subjects performed visual–verbal tasks with relative accuracy, with no errors on congruent items. The patients recovered their functional preoperative status within 3 months following surgery, with no neurological deficit, and were able to resume a normal socioprofessional life.

Anatomo-Functional Correlations

All specific cross-modal errors appearing only in intraoperative session (Task B) and not in pre- and postoperative sessions (Task A) were induced during electrical stimulation of the left DLPFC (and, subcortically, of its fibers for 2 patients). Figure 2 shows the site locations of these specific cross-modal errors. Individual intraoperative maps and their respective legends are shown in the Figure 2*A-D*.

Discussion

For all patients, focal brain stimulation of a discrete cortical area within the left DLFPC leads to dissociated patterns of errors during the cross-modal judgment tasks. They were related to cross-modal visual–verbal skill but not picture naming (i.e., phonological and semantic production), implicated mismatched pairs but not congruent pairs, and patients produced significantly more phonological than semantic errors. The complexity of the left DLFPC and the respective neuroanatomical and neuropsychological bases of picture naming, visual–verbal processing, incongruence judgment, semantic, and phonological processing can account for these dissociated findings.

The Complexity of the Left DLPFC

The left DLPFC is implicated in complex and integrative skills such as divided attention (Johnson and Zatorre 2006; Wagner

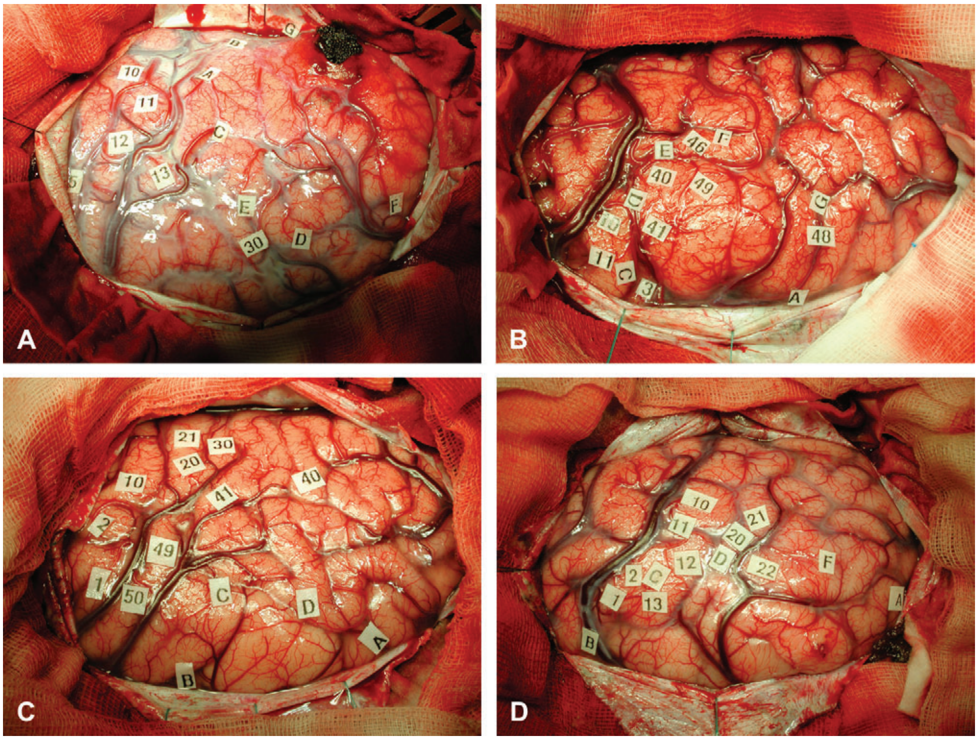

Figure 2. Intraoperative views before resection and location of specific disturbances following electrical stimulation during Task B. The letter tags demarcate the tumors identified using intraoperative ultrasonography. (*A*) Patient FV: During the surgical session, electrical stimulation in the primary somatosensory area in (5), produced a digital dysesthesia; complete speech arrest with stimulation in the ventral premotor cortex in (10) and (11), dysarthria with facial movements in the face primary motor area in (12), and semantic paraphasias in the dorsal premotor cortex in (13). In the DLPFC (30), in front of the dorsal premotor cortex, electric stimulation produced 5 specific cross-modal visual–auditory errors (1 semantic, 4 phonological) but no naming disturbance and no judgment error with congruent stimuli. (*B*) Patient PR: facial contraction was produced following electrical stimulation of the face primary motor area in (3), thumb and hand dysesthesia with stimulation of the primary somatosensory area in (10) and (11), respectively, and severe articulatory disturbances with stimulation of the ventral premotor cortex in (40), (41), (46), and (49). In addition, in (48), that is, the DLPFC (partly shifted anteriorly owing to a mass effect induced by the tumor), electrical stimulation produced 3 specific cross-modal visual–auditory errors (1 semantic and 2 phonological) but no naming difficulty and no judgment error with congruent stimuli. (*C*) Patient IJ: Electrical stimulation produced disturbances in finger movements in the primary motor area in (1); facial movements in the primary motor area in (2) and (10); anarthria in the ventral premotor cortex in (20) and (21); complete speech arrest in the pars opercularis in (30) and (41); anomia in the pars triangularis in (40), and phonemic paraphasia in the dorsal premotor cortex in (50). In the DLPFC (49), the stimulation generated 3 specific cross-modal visual–verbal errors (all phonological) but no naming error and no judgment error with congruent stimuli. (*D*) Patient CC: Electrical stimulation produced disturbances in the following areas: primary motor area of the fingers (1) and (2); primary motor area of the face (10) and (11); ventral premotor area, inducing anarthria when stimulated (20) and (21); dorsal premotor area, inducing phonemic paraphasia during stimulation (12) and (13). In (22), that is, the DLPFC, in front of the premotor cortex, electrical stimulation produced 6 specific cross-modal visual–verbal errors (5 phonological and 1 semantic) but no naming difficulty and no judgment error with congruent stimuli.

et al. 2006), top-down attention control (Loose et al. 2006; Vanderhasselt et al. 2006), mood regulation and cognitive integration (Caetano et al. 2005), complex causal thinking (Fugelsang and Dunbar 2005), verbal working memory (Fregni et al. 2005; Skrdlantova et al. 2005; Kho et al. 2007; Marklund et al. 2007; Osaka et al. 2007), and motor attentional preparation (Rounis et al. 2007). Because of its complex and integrative role, the implication of the left DLPFC has been studied in psychiatric syndromes such as schizophrenia and bipolar troubles. In the study of Kawagushi et al. (2005), left DLPFC dysfunction was related to auditory hallucinations in schizophrenic patients compared with normal control subjects and schizophrenic patients without auditory hallucinations. In the structural MRI study of Prasad (2005), the left DLPFC size predicted functional outcome at 1 year in first-episode schizophrenia. Hypoactivity of the left and right DLPFC during cognitive tasks is among the most consistent findings in schizophrenia (Papiol et al. 2007; Salgado-Pineda et al. 2007).

Using fMRI studies, Heekeren et al. (2004) proposed a model of the left DLPFC, suggesting that this structure may contain a general mechanism for integrating perceptual information. They hypothesized a relatively homogeneous population of neurons in the left DLPFC, defined as a perceptual decision-making module. According to them, the involvement of the left DLPFC in decision-making processes generalizes across different tasks, indicating that this prefrontal region has general decision-making functions, independent of stimulus and response modalities. The left DLPFC appears to be involved in the planning of responses to environmental stimuli, in making decisions requiring multimodal information, in discriminating between good and poor decisions (Krawczyk 2002; Wood and Grafman 2003), in controlling unpleasant emotions (Herwig et al. 2007) and risk-taking behaviors (Fecteau et al. 2007). Whereas the ventromedial prefrontal cortex is involved in learning novel situations and temporal novelty decisions, the left DLPFC is involved in behaviors relying on familiar situations and in temporal recency decisions (Sirigu et al. 1995; Koechlin et al. 2000; Dudukovic and Wagner 2007).

The model proposed by Heekeren et al., suggesting that the left DLPFC plays a significant role in perceptual attention and judgment, is "conversely" supported by studies of schizophrenic patients, in which perceptual auditory decision-making impairments (hallucinations) correlate with left

Table 2.
Pre-, intra-, and postoperative assessment of visual–verbal tasks

Patients	FV	PR	IJ	CC
Preoperative errors (J-1)	2	3	2	2
Type of errors	−1 semantic −1 phonological	−1 semantic −2 phonological	−2 phonological	−2 phonological
Intraoperative errors during stimulation[a]	5	3	3	6
Type of errors	−1 semantic −4 phonological	−1 semantic −2 phonological	−3 phonological	−1 semantic −5 phonological
Postoperative errors (J + 6)	1	1	2	2
Type of errors	−1 phonological	−1 phonological	−1 phonological −1 semantic	−2 phonological

[a]Errors specifically committed during the electrical stimulation and not the day before nor 6 days after surgery.

Table 3
Detailed intraoperative assessment of visual–verbal Task B

Patients	FV	PR	IJ	CC
DLPFC stimulation	3/3 phonological incongruent 1/3 semantic incongruent 0/3 congruent	2/3 phonological incongruent 1/3 semantic incongruent 0/3 congruent	3/3 phonological incongruent 0/3 semantic incongruent 0/3 congruent	3/3 phonological incongruent 1/3 semantic incongruent 0/3 congruent
Other prefrontal site stimulation	0/6 phonological incongruent 0/6 semantic incongruent 0/6 congruent	0/6 phonological incongruent 0/6 semantic incongruent 0/6 congruent	0/6 phonological incongruent 0/6 semantic incongruent 0/6 congruent	0/6 phonological incongruent 0/6 semantic incongruent 0/6 congruent
Subcortical DLPFC stimulation	1/3 phonological incongruent	—	—	2/3 phonological incongruent
No stimulation	20/20 correct incongruent and congruent responses	23/23 correct incongruent and congruent responses	23/23 correct incongruent and congruent responses	20/20 correct incongruent and congruent responses

DLPFC dysfunction. In our study, the stimulation of a discrete cortical area within the left DLPFC impaired the 4 patients' auditory–visual judgment during a task involving familiar stimuli that they perfectly discriminated the day before and 6 days after surgery.

The DLPFC is obviously part of a complex network and its stimulation probably produces distal effects via connected pathways, as suggested by the observation of 2 patients (FV and CC). However, it was previously demonstrated that a resection in the vicinity of "eloquent" areas detected by electrical stimulation might induce permanent deficits (Haglund et al. 1994). Thus, sites eliciting speech production and/or naming disturbances when stimulated have not been mapped for cross-modal processing. Their mapping was of no use for patients, and as "eloquent" sites, they could not be removed. Due to ethical study limitation, we did not test the involvement in cross-modal judgment of frontal sites implicated in speech production (especially the inferior frontal gyrus). Thus, we can only claim that at least a discrete area within the left DLPFC is essential for cross-modal judgment. It is very likely that the DLPFC located by intraoperative mapping is an epicenter essential for cross-modal processing, even if belonging to a large-scale distributed network. Future studies will analyze the role of other language frontal areas and parietotemporal regions in incongruence judgment.

Cross-Modal Judgment Errors Induced by Cortical Stimulation

The stimulation of one discrete cortical area in the DLPFC induced no speech disturbance during the naming task but generated a specific cross-modal visual–verbal deficit. In previous studies using picture-naming tasks (Johnson and Ojemann 2000; Duffau et al. 2003; Duffau 2005), electrical stimulation in various brain areas induced diverse verbal disturbances such as phonemic and semantic paraphasias, planning disorders, anomia, and articulatory disorders. The wide distribution of brain areas disturbed by electrical stimulation during picture naming can be explained by the complexity of the naming tasks. Indeed, picture naming requires the visual identification of distinct objects (e.g., animates, nonanimates, and tools), long-term memory word retrieval, phonological, and motor planning, that is, successive visual and verbal processing (Damasio et al. 2004). In contrast, the cross-modal picture–word task requires simultaneous visual and verbal processing. The dissociation observed between picture naming and cross-modal judgment in all 4 patients suggests that electrical stimulation of a discrete cortical area within the DLPFC can inhibit the simultaneous processing of visual–verbal information without disturbing the successive visual and verbal processing recruiting a larger network.

Dissociation between Congruent and Incongruent Conditions

Cross-modal visual–verbal errors were elicited only in the incongruent condition. Neurofunctional imaging studies have shown that a large-scale network underlies congruence processing, especially the left superior temporal sulcus, inferior parietal sulcus, and posterior insula (Calvert et al. 2001). As none of these areas was stimulated during the intraoperative sessions, it is not surprising that the patients correctly processed the congruent items. In contrast, incongruent conditions generate a conflict between the semantic or phonological cues evoked by the visual stimuli and those evoked by the verbal stimuli. As shown by ERP and fMRI studies, the prefrontal cortex is particularly involved in the detection of incongruent visual–verbal stimuli (McGurk and MacDonald 1976; Wang et al. 2002; Jones and Callan 2003; D'Arcy et al. 2004). In our patients, electrical stimulation of the DLPFC temporarily interfered with incongruence judgment, generating a brief virtual lesion effect and revealing the essential contribution of this area. These findings are consistent with the executive functions of the prefrontal cortex, which can be activated by cognitive conflicts (Fink et al. 2000; Luu et al. 2000). Noninvasive rTMS of the DLPFC produces disturbances in selective attention and congruence judgments during the Stroop task (Vanderhasselt et al. 2006). It can be hypothesized that focal intraoperative electrical stimulations of a prefrontal area essential to the cognitive voluntary control of interference temporarily inactivated the perception of the discrepancies between visual and verbal stimuli, generating judgment errors.

Dissociation between Phonological and Semantic Errors

In the 4 patients, electrical stimulation of the left DLPFC globally spared semantic processing while altering phoneme discrimination. As far as language is concerned, semantic and phonological incongruent pairs require different processing. The semantic incongruent words are conceptually close to the visual target and do not share the same phonological cues (e.g., "elephant/mammoth"). In contrast, the phonological incongruent items share the similar syllabic and rhyming patterns and only differ from the target words by one vocalic or consonant phoneme ("**b**rosse/**p**rosse", "**in**spirateur/**a**spirateur"). In order to judge whether the phonological form of an evocated verbal stimulus and one that is heard are similar or not, patients must separate simultaneous verbal (evocated and heard) stimuli, compare their phonemes, and perform a fine-grained phonemic judgment.

Within the brain, phonetic and semantic processing does not involve the same networks. Using phonetic processing tasks (discrimination of consonants and phoneme monitoring) with positron emission tomography technique, Zatorre et al. (1996) showed that each phonetic condition revealed increased cerebral blood flow in the left frontal lobe, at the limit of Broca's area and the motor cortex. Interestingly, in a second experiment, they showed that this region was not activated by a semantic judgment task. Simmons et al. (2005) asked subjects to determine which written words belong to the same category (2 out of 3) and they showed that the inferior prefrontal cortex, the left middle frontal gyrus, the left angular gyrus, and the anterior cingulate gyrus are vital structures for subjects to make a decision on word meaning. In a recent study, Rizzo et al. (2007) using rTMS asked subjects to match idiomatic versus literal sentences and pictures. They showed that both right and left DLPFC are involved in idiomatic (i.e., abstract and metaphoric meaning) and not literal (i.e., highly semantic) interpretation. As the semantically noncongruent items of our cross-modal task are close to the Rizzo's study literal sentences, we can argue that stimulation of left DLPFC does not disturb this simple semantic process.

Our findings support the existence of distinct brain networks underlying semantic/phonological global processing versus phonological/fined-grained processing. They suggest that the inhibition of a discrete area within the left dorsolateral prefrontal cortex disturb the visual/phonological "segmental" judgment without altering the semantic and "global" matching perception.

Conclusion

By a specific methodological procedure (cortical electrical stimulation in awake patients), the present study confirms that prefrontal cortex is involved in cross-modal visual–verbal processing. Moreover, it shows that the left dorsolateral prefrontal cortex is specifically involved in incongruent phonological visual–verbal matching judgment. Electrical stimulation temporarily inhibits the segmental phonological judgment, generating a brief "virtual lesion" effect.

The implication is of great theoretical and clinical interest. The patient's preservation of cross-modal processing dramatically improves the quality of language, attention, and perception. Future research will explore cross-modal processing in other brain areas using the same pre-, intra-, and postoperative assessments. Methodologically, despite limitations due to ethical restrictions, the intraoperative electrical mapping has an accurate spatial resolution, which is better than those of ERP and fMRI. Thus, the data based on the direct electrical stimulation methods are especially useful to define precise functions of brain areas.

Notes

We thank Magali Boibieux and Sylvain Mottet for program creation and implementation, Marie-Thérèse Rigoard for assistance during pre-, intra-, and postoperative sessions and data analyses, and Yvane Wiart for her review of the English version. *Conflict of Interest*: None declared.

Address correspondence to email: monique.plaza@univ-paris5.fr.

References

Booth JR, Burman DD, Meyer JR, Gitelman DR, Parrish TD, Mesulam MM. 2005. Functional anatomy of intra- and cross-modal lexical tasks. Neuroimage. 16:7–22.

Caetano SC, Fonseca M, Olvera RL, Nicoletti M, Hatch JP, Stanley JA, Hunter K, Lafer B, Pliszka SR, Soares JC. 2005. Proton spectroscopy study of the left dorsolateral prefrontal cortex in pediatric depressed patients. Neurosci Lett. 384(3):321–326.

Calvert GA. 2001. Crossmodal processing in the human brain: insights from functional neuroimaging studies. Cereb Cortex. 11(12): 1110–1123.

Calvert GA, Hansen PC, Iversen SD, Brammer MJ. 2001. Detection of multisensory integration sites by application of electrophysiological criteria to the BOLD response. Neuroimage. 14:427–438.

Damasio H, Tranel D, Grabowski T, Adolphs R, Damasio A. 2004. Neural systems behind word and concept retrieval. Cognition. 92:179–229.

D'Arcy R, Connolly J, Service E, Hawco C, Houlihan M. 2004. Separating phonological and semantic processing in auditory sentence processing: A high resolution event-related brain potential study. Hum Brain Mapp. 22(1):40–51.

Dudukovic NM, Wagner AD. 2007. Goal-dependent modulation of declarative memory: neural correlates of temporal recency decisions and novelty decisions. Neuropsychologia. 45(11):2608–2620.

Duffau H. 2005. Lessons from brain mapping in surgery for low-grade glioma: insights into association between tumor and brain plasticity. Lancet Neurol. 4(8):476–486.

Duffau H, Capelle L, Denvil D, Gatignol P, Sichez N, Lopes M, Sichez JP, Van Effenterre R. 2003. The role of dominant premotor cortex in language: a study using intraoperative functional mapping in awake patients. Neuroimage. 20:1903–1914.

Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. 2005. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain. 128:797–810.

Fecteau S, Pascual-Leone A, Zald DH, Liguori P, Théoret H, Boggio PS, Fregni F. 2007. Activation of prefrontal cortex by transcranial current stimulation reduces appetite for risk during ambiguous decision making. J Neurosci. 27(23):6212–6218.

Fink GR, Marshall JC, Halligan CD, Frith J, Driver RS, Frackowiak RS, Dolan RJ. 2000. The neural consequences of conflict between intention and the senses. Brain. 122:497-512.
Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MT, Paulus W, et al. 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 166(1):23-30.
Fugelsang JA, Dunbar KN. 2005. Brain-based mechanisms underlying complex causal thinking. Neuropsychologia. 43(8):1203-1214.
Gatignol P, Capelle L, Le Bihan R, Duffau H. 2004. Double dissociation between picture naming and comprehension: an electrostimulation study. Neuroreport. 15(1):191-195.
Goodglass H, Kaplan E. 1983. Boston diagnostic aphasia examination. San Antonio (TX): The Psychological Corporation.
Heekeren HR, Marrett S, Bandettini PA, Ungerleider LG. 2004. A general mechanism for perceptual decision-making in the human brain. Nature. 431:859-862.
Herwig U, Baumgarner T, Kaffenberger T, Brühl A, Kottlow M, Schreiter-Gasser U, Abler B, Jäncke L, Rufer M. 2007. Forthcoming. Modulation of anticipatory emotion and perception processing by cognitive control. Neuroimage. 37(2):652-662
Haglund M, Berger M, Shamseldin M, Lettich E, Ojemann G. 2004. Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery. 34(4):567-576.
Johnson JA, Zatorre RJ. 2006. Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. Neuroimage. 31(4):1673-1681.
Johnson MD, Ojemann GA. 2000. The role of human thalamus in language and memory: evidence from electrophysiological studies. Brain Cogn. 42(2):218-230.
Jones JA, Callan DE. 2003. Brain activity during audiovisual speech perception: An *f*MRI study of the McGurk effect. Cogn Neurosci Neuropsychol. 14(8):1129-1133.
Kawagushi S, Ukai S, Shinosaki K, Ishii R, Yamamoto M, Ogawa A, Mizuno-Matsumoto Y, Fujita N, Yoshimine T, Takeda M. 2005. Information processing flow and neural activations in the dorsolateral prefrontal cortex in the Stroop task in schizophrenic patients. A spatially filtered MEG analysis with high temporal and spatial resolution. Neuropsychobiol. 51(4):191-203.
Kho KH, Rutten GJ, Leijten FS, Van der Schaaf A, van Rijen PC, Ramsey NF. 2007. Working memory deficits after resection of the dorsolateral prefrontal cortex predicted by functional magnetic resonance imaging and electrocortical stimulation mapping. J Neurosurg. 106(6 Suppl):501-505.
Koechlin E, Corrado G, Pietrini P, Grafman J. 2000. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proc Natl Acad Sci USA. 97:7651-7656.
Krawczyk DC. 2002. Contribution of the prefrontal cortex to the neural basis of human decision making. Neurosci Biobehav Rev. 26: 631-664.
Laurienti PJ, Kraft RA, Maldjian JA, Burdette JH, Wallace MT. 2004. Semantic congruence is a critical factor in multisensory behavioral performance. Exp Brain Res. 158(4):405-414.
Loose R, Kaufmann C, Tucha O, Auer DP, Lange KW. 2006. Neural networks of response shifting: influence of task speed and stimulus material. Brain Res. 1090(1):146-155.
Luu P, Flaisch T, Tucker DM. 2000. Medial frontal cortex in action monitoring. J Neurosci. 20:464-469.
Marklund P, Fransson P, Cabeza R, Petersson KM, Ingvar M, Nyberg L. 2007. Sustent and transient neural modulations in prefrontal cortex related to declarative long-term memory, working memory, and attention. Cortex. 43(1):22-37.
McGurk H, MacDonald J. 1976. Hearing lips and seeing voices. Nature. 264:746-748.
Metz-Lutz MN, Kremin H, Deloche G. 1991. Standardisation d'un test de dénomination orale: contrôle des effets de l'âge, du sexe et du niveau de scolarité chez les sujets adultes normaux. Rev Neuropsychol. 1:73-95.
Molhom S, Ritter W, Javitt DC, Foxe JJ. 2004. Multisensory visual-auditory object recognition in humans: a high-density electrical mapping study. Cereb Cortex. 14(4):452-465.
Molhom S, Sehatpour P, Mehta AD, Shpaner M, Gomez-Ramirez M, Ortigue S, Dyke JP, Schwartz Th, Foxe JJ. 2006. Audiovisual multisensory integration in superior temporal lobule revealed by human intracranial recordings. J Neurophysiol. 96(2): 721-729.
Ojemann G, Ojemann J, Lettich E, Berger M. 1989. Cortical language localization in left dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg. 71(3): 316-326.
Osaka N, Otsuka Y, Hirose N, Ikeda T, Mima T, Fukuyama H, Osaka M. 2007. Transcranial magnetic stimulation applied to left dorsolateral prefrontal cortex diruptes verbal working memory performance in humans. Neurosci Lett. 418(3):232-235.
Papiol S, Molina V, Rosa A, Sanz J, Palomo T, Fananas L. 2007. Forthcoming. Effect of interleukin-1beta gene functional polymorphism on dorsolateral prefrontal cortex activity in scizophrenic patients. Am J Med Genet B Neuropsychiatr Genet.
Prasad KM. 2005. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. Psychiatry Res. 140(2):147-155.
Rizzo S, Sandrini M, Papagno C. 2007. The dorsolateral prefrontal cortex in idiom interpretaiton: an rTMS study. Brain Res Bull. 71(5): 523-528.
Ross LA, Saint-Amour D, Leavitt VM, Javitt DC, Foxe JJ. 2007. Do you see what I am saying? Exploring visual enhancement of speech comprehension in noisy environments. Cerebral Cortex. 17(5): 1147-1153.
Rounis E, Yarrow K, Rothwell JC. 2007. Effects of rTMS conditioning over the fronto-parietal netwok on motor versus visual attention. J Cogn Neurosci. 19(3):513-524.
Saint-Amour D, De Sanctis P, Molhom S, Ritter W, Foxe JJ. 2007. Seeing voices: High-density electrical mapping and source-analysis of the multisensory mismatch negativity evoked during the McGurk illusion. Neuropsychologia. 45(3):587-597.
Salgado-Pineda P, Caclin A, Baeza I, Junqué C, Bernardo M, Blin O, Fonlupt P. 2007. Schizophrenia and frontal cortex: where does it fail? Schizophr Res. 91(1-3):73-81.
Simmons A, Miller D, Feinstein JS, Goldberg TE, Paulus MP. 2005. Left inferior prefrontal cortex activation during a semantic decision-making task predicts the degree of semantic organization. Neuroimage. 28:30-38.
Sirigu A, Zalla T, Pillon B, Grafman J, Agid Y, Dubois B. 1995. Selective impairments in managerial knowledge following prefrontal cortex damage. Cortex. 31:301-316.
Skrdlantova L, Horacek J, Dockery C, Lukavsky J, Kopecek M, Preiss M, Novak T, Hoschl C. 2005. The influence of low-frequency left prefrontal repetitive transcranial magnetic stimulation on memory for words but not for faces. Physiol Res. 54(1):123-128.
Taylor K, Moss H, Stamatakis E, Tyler L. 2006. Binding crossmodal object features in perirhinal cortex. Proc Natl Acad Sci USA. 103(21): 8239-8244.
Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Levy R, Dubois B, Bartolomeo P. 2005. Direct evidence for a parietal-frontal pathway subserving spatial awareness in humans. Science. 309: 2226-2228.
Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'haenen H. 2006. The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. Exp Brain Res. 169(2):279-282.
Wagner M, Rihs TA, Mosimann UP, Fisch H, Schlaepfer TE. 2006. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex affects divided attention immediately after cessation of stimulation. Psychiatry Res. 40(4):315-321.
Wang Y, Wang H, Cui L, Tian S, Zhang Y. 2002. The N270 component of the event-related potential reflects supramodal conflict processing in humans. Neurosci Lett. 332(1):25-28.
Wood JN, Grafman J. 2003. Human prefrontal cortex: processing and representational perspectives. Nature Neurosci. 4:139-147.
Zatorre RJ, Evans AC, Meyer E, Gjedde A. 1996. PET studies of phonetic processing of speech: Review, replication and reanalysis. Cereb Cortex. 6(1):21-30.