Single-pulse electrical stimulation identifies epileptogenic frontal cortex in the human brain

A. Valentín, MD, PhD; G. Alarcón, MD, PhD; J.J. García-Seoane, MD, PhD; M.E. Lacruz, BSc; S.D. Nayak, MD; M. Honavar, MD, FRCPath; R.P. Selway, FRCS; C.D. Binnie, MD, FRCP; and C.E. Polkey, PhD, FRCS

Abstract—*Objective:* To assess the value of single-pulse electrical stimulation (SPES) to identify frontal epileptogenic cortex during presurgical assessment. *Methods:* SPES (1-millisecond pulses, 4 to 8 mA, 0.1 Hz) has been used during chronic recordings in 30 patients with intracranial electrodes in the frontal lobes. As a result of presurgical assessment, 17 patients were considered to have frontal epilepsy and 13 extrafrontal epilepsy. *Results:* Two types of responses to SPES were seen: 1) early responses: starting immediately after the stimulus and considered as normal responses; 2) late responses: two types of responses seen in some areas after the initial early response: a) delayed responses: spikes or sharp waves occurring between 100 milliseconds and 1 second after stimulation. Frontal delayed responses were seen in 11 frontal patients and 1 extrafrontal patient, whereas extrafrontal delayed responses were seen in 1 frontal and 10 extrafrontal patients. b) Repetitive responses: two or more consecutive sharp-and-slow-wave complexes, each resembling the initial early response. Repetitive responses were seen only when stimulating the frontal lobes of 10 frontal patients. Among the 17 frontal patients, 13 had late responses exclusively in the epileptogenic frontal lobe, whereas only 3 showed them in both frontal lobes. Frontal late responses were associated with neuropathologic abnormalities, and complete resection of abnormal SPES areas was associated with good postsurgical seizure outcome. *Conclusions:* Single-pulse electrical stimulation (SPES) could be an important additional investigation during presurgical assessment to identify frontal epileptogenicity. SPES can be useful in patients who have widespread or multiple epileptogenic areas, normal neuroimaging, or few seizures during telemetry.

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Frontal lobe epilepsy is often resistant to medical treatment, accounting for as many of 18% of the patients who undergo surgery for epilepsy.[1,2] However, surgical outcome with regard to seizure control in frontal lobe epilepsy is generally poorer than in temporal lobe epilepsy.[2] Whereas the best predictor for a favorable surgical outcome in frontal lobe epilepsy appears to be the presence of a focal abnormality on neuroimaging,[3,4] no clear guidelines exist for the assessment of patients where neuroimaging abnormalities are widespread, multiple, or absent. In frontal lobe epilepsy, it can be difficult to identify the cortical region responsible for seizure origin,[5,6] and intracranial EEG recordings may be required to identify the onset of spontaneous seizures. Nevertheless, assessment of frontal lobe epilepsy with intracranial recordings remains difficult because widespread EEG changes are commonly seen at seizure onset, possibly owing to rapid seizure propagation, and because there is no specific a priori candidate site for implantation in the absence of a focal lesion on neuroimaging. In addition, the frontal lobe is the largest brain lobe, and the number of implanted electrodes is necessarily limited, which sometimes leads to inadequate spatial sampling. We have recently reported that cortical responses to single-pulse electrical stimulation (SPES) can identify epileptogenic cortex in the human brain in vivo.[7] Since then, SPES has become part of the protocol for presurgical assessment with intracranial recordings at King's College Hospital (London, UK). In the current study, we have assessed the value of SPES to identify frontal epileptogenic cortex by comparing responses to SPES in the epileptogenic frontal lobe with responses in the nonepileptogenic frontal lobe of the same patient and with frontal lobe responses in patients with extrafrontal epilepsy.

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From the Departments of Clinical Neuroscience (Drs. Valentín, Alarcón, Nayak, and Binnie, M.E. Lacruz), Clinical Neuropathology (Dr. Honavar), and Neurosurgery (Dr. Selway), Guy's, King's, and St. Thomas' School of Medicine, King's College Hospital, London, UK; Facultad de Medicina (Dr. García-Seoane), Universidad Complutense, Madrid, Spain; and Department of Neurology (Dr. Nayak) Kovai Medical Centre and Hospital, Coimbatore, India.

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Address correspondence and reprint requests to Dr. G. Alarcón, Department of Clinical Neurophysiology, King's College Hospital, London, SE5 9RS, UK; e-mail: galarcon@aol.com

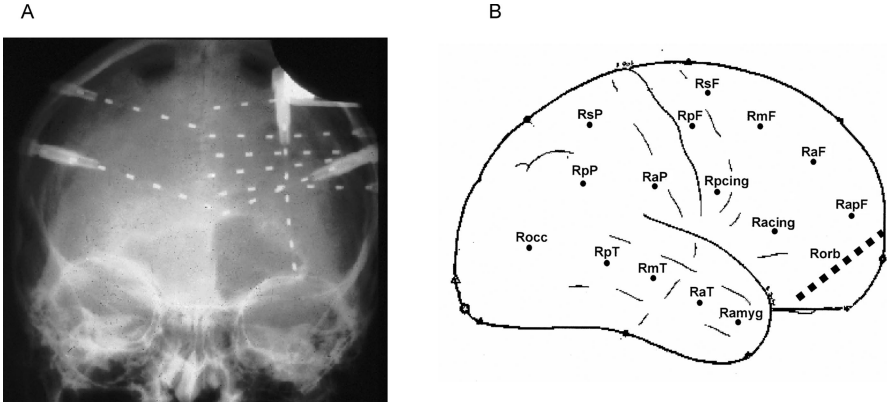

Figure 1. Intracerebral (depth) electrode bundles. (A) Frontal radiograph showing implanted intracerebral (depth) electrode bundles. (B) Drawing showing the most common locations for intracerebral electrode bundles in the right hemisphere. Each dot represents the position of the section of an intracerebral electrode bundle introduced laterally. The dashed line represents the approximate direction of the orbitofrontal electrode bundle. Ramyg = right amygdala; RaT = right anterior temporal; RmT = right midtemporal; RpT = right posterior temporal; Rocc = right occipital; RapF = right anterior polar frontal; RaF = right anterior frontal; RmF = right midfrontal; RpF = right posterior frontal; RsF = right superior frontal; Rorb = right orbitofrontal; Rpcing = right posterior cingulate; Racing = right anterior cingulate; RsP = right superior parietal; RaP = right anterior parietal; RpP = right posterior parietal. When symmetric locations were studied in the left hemisphere, labels of left-sided electrodes will start with L instead of R.

Methods. *Subjects.* We have studied 30 consecutive adult patients (18 men, 12 women; median age 34 years, range 18 to 57 years) who had frontal intracranial electrodes during presurgical evaluation for the treatment of their epilepsy in the Department of Clinical Neurophysiology at King's College Hospital. Patients had medically refractory epilepsy and were admitted for video-EEG monitoring with intracranial electrodes because reliable localization of the epileptogenic zone had not been achieved by noninvasive tests. Patients with previous resective surgery for epilepsy in the frontal lobe were excluded from this study. All patients were fully informed of the nature of the research and gave informed consent, according to the Declaration of Helsinki (1964). The experimental procedure and consent form have been approved by the Ethical Committee of King's College Hospital (reference no. 99-017).

Electrode placement. Subdural or intracerebral (depth) electrodes were implanted in all 30 patients. Twenty-one patients had electrodes located in frontal and temporal areas, four patients had electrodes located in frontal areas only, three had electrodes located in frontal and parietal areas, and two had electrodes located in frontal, temporal, and parietal areas. Twenty-five patients had electrodes implanted bilaterally, and five had electrodes restricted to one hemisphere. Patients had frontal electrodes implanted 1) because frontal lobe epilepsy was suspected but localization or lateralization of seizure onset required confirmation or 2) to distinguish between frontal and extrafrontal (mainly temporal) epilepsy when noninvasive diagnostic tests yielded conflicting results. The type, number, and position of the electrodes were determined by the location of the suspected epileptogenic zone in each patient, according to findings from clinical history, neuroimaging, neuropsychology, and scalp EEG recordings. The selection criteria and implantation procedure have been described elsewhere.[8]

Subdural electrodes. Electrode strips or mats (AdTech Medical Instruments Corp., WI) were used in 12 patients. Each strip consisted of a single row of four to eight platinum disk electrodes spaced at 10 mm between centers. The disks were embedded in a 0.7-mm-thick polyurethane strip that overlapped the edges leaving a diameter of 2.3 mm exposed and recessed approximately 0.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32, or 64 similar platinum electrodes.

Among the 12 patients with subdural electrodes, 5 had unilateral frontal and extrafrontal electrodes, 3 had bilateral frontal and extrafrontal electrodes, 1 had bilateral frontal and unilateral extrafrontal electrodes, and 3 had bilateral extrafrontal and unilateral frontal electrodes (see table E-1 on the *Neurology* Web site at www.neurology.org).

Intracerebral (depth) electrodes. In 18 patients, bilateral multicontact flexible bundles of depth electrodes (AdTech Medical Instruments Corp.) were implanted stereotactically under MRI guidance (figure 1). The electrodes consisted of 6 to 10 cylindrical 2.3-mm-long platinum contacts separated by 5 mm between centers of adjacent electrodes of the same bundle. Among these 18 patients, 12 had electrodes located bilaterally in frontal and extrafrontal structures, 3 patients had bilateral frontal electrodes and unilateral extrafrontal electrodes, and 3 patients had bilateral electrodes restricted to frontal structures (see table E-1). Figure 1B shows a template with the most common locations for intracerebral electrodes and the electrode labeling to be used in the figures throughout the article.

EEG recording. Recording of intracranial EEG started when the patient had recovered from the operation required for implantation, usually after 24 to 48 hours. Cable telemetry with up to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 27 patients, a Telefactor Beehive-Beekeeper system (Astro-Med, RI) was used. Data were digitized at 200 Hz with an antialiasing filter at 100 Hz and bandpass filtered (high-pass cut-off frequency at 0.3 Hz and low-pass cut-off frequency at 70 Hz). The system input range was 2 mV, and data were digitized with a 12-bit analog-to-digital converter (amplitude resolution of 0.488 μV). In the remaining three patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, UK). Data were digitized at 256 Hz and bandpass filtered (0.05 to 67 Hz). The input range was 10 mV, and data were digitized with a 16-bit analog-to-digital converter (an amplitude resolution of 0.153 μV). Data were recorded as common reference to Pz or to an intracranial electrode, and displayed in a variety of montages including common average reference.

Experimental protocol. SPES was performed between adjacent electrodes using a constant-current neurostimulator (Medelec ST10 Sensor). The experimental protocol has been fully described elsewhere.[7] In brief, electrical stimulation was carried out with monophasic single pulses of 1-millisecond duration and current intensity ranging between 4 and 8 mA (4 mA being the intensity most often used). A single pulse was delivered every 8 to 10 seconds, and EEG responses to each pulse were recorded by the electrodes not used for stimulation. Typically, for every pair of stimulating electrodes and for each polarity, a total of 10 single pulses was delivered 8 to 10 seconds apart to estimate the consistency of responses. In patients with subdural electrodes, all available contacts were used to stimulate. In patients with intracerebral recordings only pairs of electrodes located in gray matter (according to MR images obtained with the electrodes implanted) were used to stimulate. There were no obvious differences between responses to SPES recorded by subdural or depth electrodes.

Twenty-one patients did not show any behavioral, sensory, or motor response to SPES. Five patients experienced brief motor jerks in the contralateral hand, arm, or leg when frontal cortex was stimulated. Four patients had a tingling sensation or a brief jerk in the ipsilateral side of the face when stimulation through the deepest contacts of subtemporal strips was carried out, pre-

sumably due to stimulation of the cranial nerves. When this occurred, stimulus intensity was decreased or stimulation at this site was abandoned.

Classification of patients. Patients were classified presurgically as frontal or extrafrontal after completion of telemetry, according to results from the following three standard diagnostic tests: 1) neuroimaging (volumetric T1-weighted coronal and axial T2-weighted MR images and coronal fluid-attenuated inversion recovery); 2) topography of the onset of spontaneous seizures recorded during intracranial telemetry; and 3) reproduction of the patient's habitual seizures using cortical stimulation with trains of electrical pulses (biphasic 2-millisecond pulses at 50 Hz during 1 to 5 seconds). These were also the criteria used to decide the surgical procedure during routine assessment in our center. Presurgical classification of patients as frontal or extrafrontal was performed to be able to assess the value of SPES as a presurgical diagnostic technique by comparing its localizing value with results from more standard presurgical diagnostic tests. The authors involved in performing and interpreting SPES were blind to clinical history, neuroimaging findings, topography of seizure onset, and results from stimulation with trains of electrical pulses. Results from SPES were not considered for classifying patients into frontal or extrafrontal.

The site of seizure onset was determined by the position of the electrodes that showed the first EEG ictal changes. Seizure onset was identified as a clear ictal EEG pattern consisting of regular spikes, rhythmic sharp waves, spike-and-slow wave complexes, sharp-and-slow-wave complexes, rhythmic delta or theta activities, sharpened delta or theta activities, or low-amplitude high-frequency activity in the beta range. Diffuse electrodecremental events were noted but not considered for analysis, as they do not seem to be of localizing value.[9] Seizures with electrographic onset starting after the first clinical manifestations were not considered. Seizure onset was classified as 1) focal if three or less adjacent electrodes were involved at onset, 2) regional if more than three electrodes in the same lobe were involved at onset, or 3) nonlocalized if EEG changes at seizure onset were bilateral or involved more than one lobe.

For the current study, patients were classified as frontal if one of the two following criteria were met: 1) Seizure onset was clearly localized in one frontal lobe and no other test showed a focal abnormality elsewhere (15 patients); or 2) seizure onset and another standard diagnostic test clearly identified an abnormality in one frontal lobe, regardless the result of the third standard diagnostic test, which identified an abnormality elsewhere (two patients). Patients were considered as extrafrontal if 1) seizure onset was extrafrontal and no other test showed a frontal abnormality (10 patients); or 2) seizure onset was not localized, but the other two standard tests clearly identified an extrafrontal cortical abnormality (3 patients). To simplify wording, the lobe whose abnormalities determined classification according to the above criteria was called the epileptogenic lobe

Following these criteria, 17 patients were classified as frontal and 13 were considered extrafrontal.

Surgery, neuropathology, and surgical outcome. Surgery was carried out on 20 patients (10 of the 17 frontal patients and 10 of the 13 extrafrontal patients). Results from SPES were not taken into consideration for the surgical decision. Resections were guided by preoperative and intraoperative electrocorticography and by intraoperative image guidance (Stealth; Medtronic, Houston, TX). As the purpose of this study is to estimate the value of SPES for presurgical assessment of frontal patients, only patients classified as frontal were considered for correlations with neuropathology and surgical outcome. Among the 10 operated frontal patients, focal frontal resections were carried out in 8, 2 of whom also had functionally eloquent areas treated with multiple subpial transections. Among the remaining two patients, one underwent an extensive frontal lobectomy including primary motor cortex of the hand but sparing regions involved in speech and leg function. The last frontal patient had a hypothalamic hamartoma and underwent a stereotactically guided percutaneous thermocoagulation under local anesthesia without surgical treatment of the frontal lobe.[10]

All resected specimens were fixed in formalin and serially sliced. The slices were processed to paraffin. In specimens with no macroscopic abnormality, all the slices were processed. When a macroscopic lesion was noted, blocks were taken from the lesion, from the margins of the specimen, and from slices adjacent to the lesion. Sections were stained with hematoxylin and eosin, luxol fast blue/cresyl violet, the silver impregnation method of Glees and Marsland, and immunocytochemistry was carried out by the avidin/biotin complex method for glial fibrillary acidic protein (DAKO polyclonal, 1:1,250; Carpinteria, CA) and neurofilament 200 kD (DAKO monoclonal, 1:800). Archived slides from all the patients were reviewed.

Surgical outcome was determined at regular postoperative follow-up assessments by authors blind to results of SPES. Surgical outcome was classified in four grades according to the following criteria, which are based largely on Engel's classification[11]: Grade I, free of disabling seizures; Grade II, almost seizure-free (three or fewer diurnal or nocturnal seizures per year); Grade III, worthwhile improvement (but more than three diurnal or nocturnal seizures per year); and Grade IV, no improvement. For analysis, Grades I and II were considered as favorable surgical outcome, whereas Grades III and IV were considered poor.

Statistical analysis. Data analysis was carried out with the Statistical Package for Social Sciences 10.0 (SPSS, Chicago, IL). The association between stimulation and delayed responses was established by comparing the occurrence of any spikes during 1 second before and 1 second after each stimulation. It was assumed that spikes were a response to stimulation if the number of stimuli showing spikes during the second following stimulation was greater than the number of stimuli showing spikes during the second prior to stimulation with $p < 0.05$ (two-tailed sign test). In the areas with frequent interictal activity that was similar to delayed responses, stimulation was repeated on the same or on a different day to decrease the probability of false positives. Associations between responses to SPES and epileptogenic lobe or surgical outcome were established by Yates corrected χ^2 test or Fisher exact test. Differences were considered significant if $p < 0.05$ (two tailed).

Results. *Patient characteristics.* Seventeen patients were classified as frontal and 13 as extrafrontal. Patients' findings with regard to neuroimaging, seizure onset, and stimulation with trains of electrical pulses can be seen in table E-2.

Neuroimaging obtained from all 30 patients showed a normal MRI in 15, mesial temporal sclerosis in 7, areas of focal cortical dysplasia in the frontal lobe in 2, a frontal tumor in 1, an extensive old infarct affecting the frontal lobe in 1, parietal tumors in 2, and hypothalamic hamartomata in 2 patients.

Among the 17 frontal patients, 3 had focal and 14 had regional seizure onset in the frontal lobe. Among the 13 extrafrontal patients, 3 had nonlocalized seizure onset, 2 had focal or regional parietal seizure onset, 3 patients had regional temporal seizure onset, and 5 had focal temporal seizure onset. Only 17.6% of frontal patients (3/17) showed a clear focal seizure onset, whereas this proportion was higher among extrafrontal patients (6/13 or 46.2%) and particularly among patients with a temporal onset (5/8 or 62.5%).

Stimulation with 50-Hz trains of electrical pulses was performed in 16 frontal and in 4 extrafrontal patients. The patient's habitual seizures were induced by stimulation in 12 frontal and in 2 extrafrontal patients.

Two frontal patients had MRI lesions outside the frontal lobe. One had a parietal tumor and the other one had a hypothalamic hamartoma. Both patients were considered frontal because most of their spontaneous seizures showed frontal onset and their seizures could be evoked by stimulating with trains of pulses in the area of seizure onset.

Cortical responses to SPES. Two main types of cortical responses were evoked by the stimuli:

Early responses. These responses usually consisted of a sharp deflection seen immediately after the stimulus

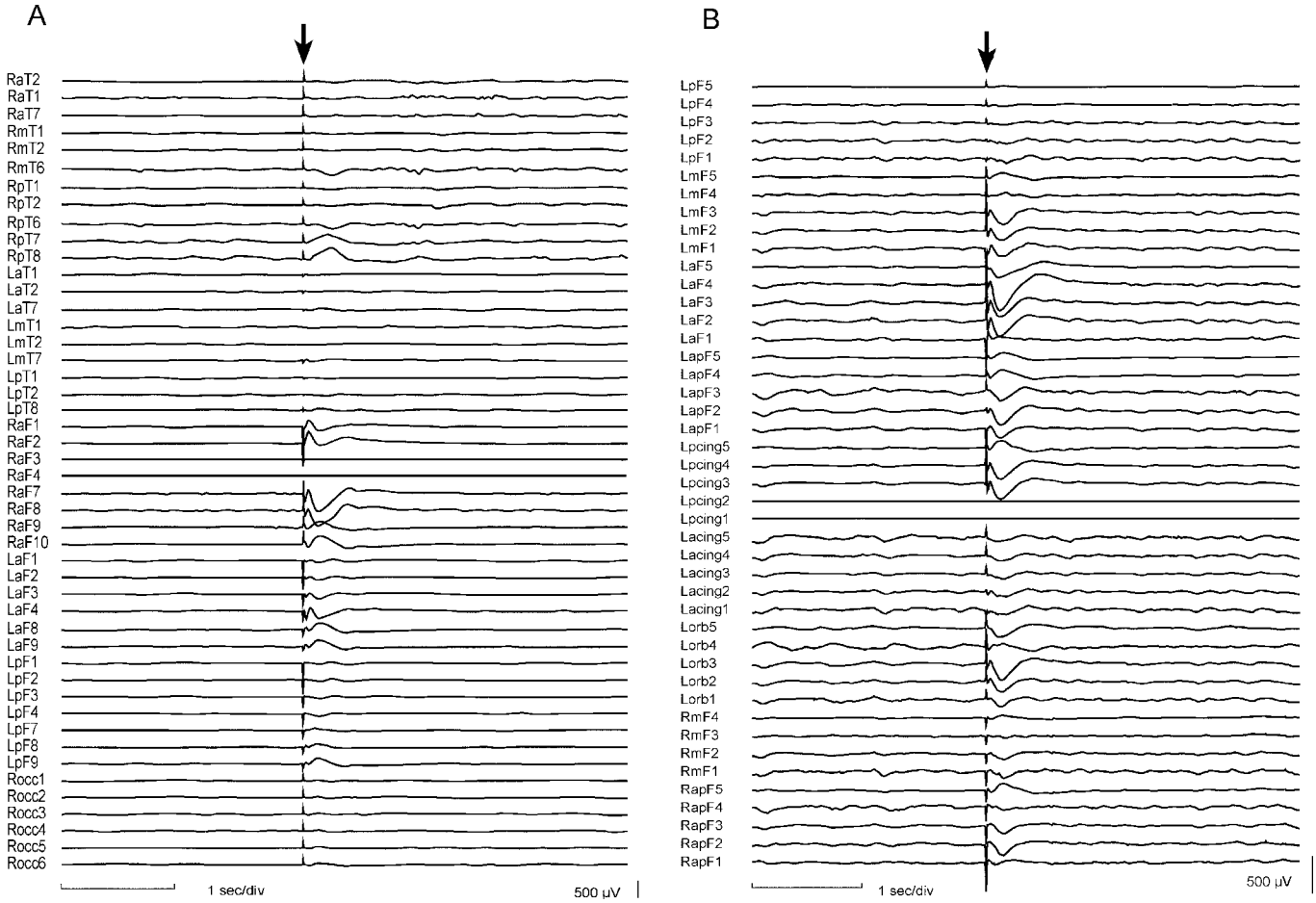

Figure 2. Early responses evoked by single-pulse electrical stimulation in the frontal lobe. (A) Early responses seen when stimulating electrodes 3 and 4 of the right anterior frontal electrode bundle (RaF 3 and 4, shown as flat traces) in an extrafrontal patient (Patient 21). Recordings have been displayed in common average reference. (B) Early responses seen when stimulating the deepest electrodes of the left posterior cingulate electrode bundle (Rpcing1 and 2) in a frontal patient (Patient 11). Recordings have been displayed in common reference to Pz. Both recordings have similar time calibration but different gain. Both patients had intracerebral (depth) electrodes. In this and subsequent figures, arrows indicate the stimulation artifact. For intracerebral (depth) electrode bundles, electrode 1 was the most distal electrode to the insertion burr hole. Electrode positions and labels are as shown in figure 1B.

artifact or occasionally merging with it, followed by a slow wave. The amplitude of early responses depended on stimulation intensity. As in our previous study,[7] early responses were seen in all patients when stimulating at most locations and were therefore considered to be normal responses of the cortex to SPES. In all 22 patients who had electrodes placed in both frontal lobes, bilateral early responses could be recorded when frontal structures were stimulated unilaterally, suggesting the presence of functional connections between both frontal lobes (figure 2A, extrafrontal patient; figure 2B, frontal patient). No obvious differences were found between the amplitude or the distribution of early responses in the epileptogenic lobe and elsewhere.

Late responses. These were cortical responses arising after the early response. Two types of late responses were seen when specific areas were stimulated:

Delayed responses. These responses were similar to those previously described by our group.[7] Namely, delayed responses consisted of spikes or spike-and-slow-wave complexes that resembled epileptiform discharges and were seen with a latency of >100 milliseconds and <1 second after the stimulus artifact (figure 3). Delayed responses were not always seen after every identical stimulus. As delayed responses were often similar to spontaneous interictal discharges, a two-tailed sign test was used to differentiate between presence of delayed responses and random occurrence of interictal activity (see Methods). When the stimulus intensity was increased, the morphology of delayed responses was not clearly modified, but a higher probability of occurrence was observed, and in some patients, bursts of spikes could be evoked with a single stimulus. We have previously established that in temporal patients, the cortical areas where delayed responses are recorded tend to coincide with areas showing seizure onset regardless of the area stimulated to induce such responses.[7] The location and distribution of delayed responses seen in frontal patients are shown in table 1.

Delayed responses were exclusively seen within the epileptogenic frontal lobe in 11 patients of the 17 considered as frontal. In addition, one frontal patient had delayed responses seen within the epileptogenic frontal lobe and in the ipsilateral temporal lobe. Six extrafrontal patients had delayed responses in the epileptogenic temporal lobe, two

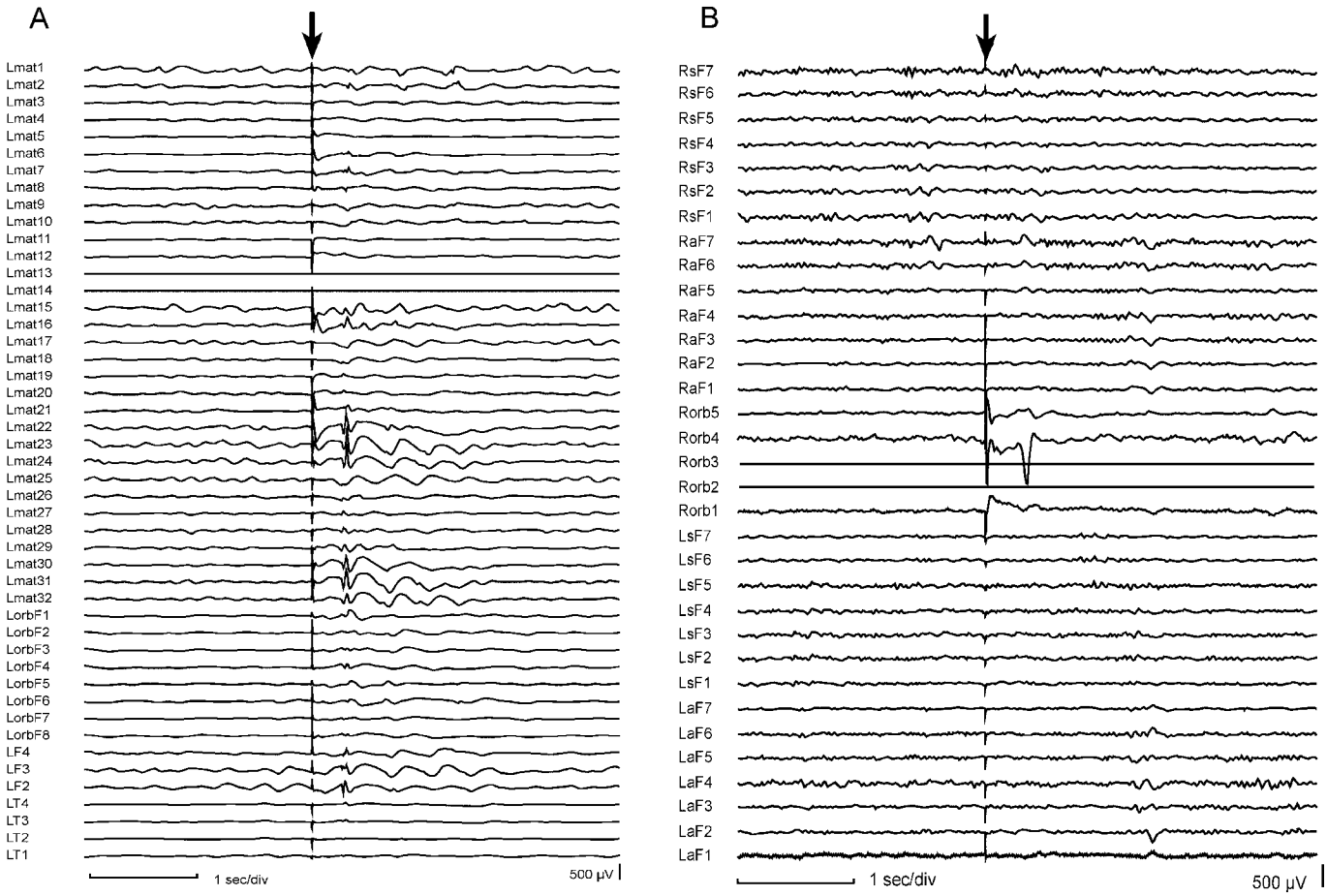

Figure 3. Delayed responses evoked by single-pulse electrical stimulation in the frontal lobe. (A) Regional delayed responses seen at the lateral convexity of the frontal lobe when stimulation was performed through contacts 13 and 14 of a 32-contact mat in Patient 12. Recordings have been displayed in common reference to Pz. For strip electrodes, electrode 1 was the most distal electrode to the insertion burr hole. (B) Focal delayed responses seen at electrode 4 of the orbitofrontal electrode bundle (Rorb4) when stimulating through electrodes 2 and 3 of the same bundle (Rorb2 and 3) in Patient 1. Recordings have been displayed in common average reference. Both recordings have similar time calibration but different gain. Lmat = left 32-contact mat; LorbF = left orbito-frontal strip; LF = left frontal strip; LT = left temporal strip. Electrode positions and labels for (B) are as shown in figure 1B.

had independent delayed responses in both temporal lobes, and two had delayed responses in the epileptogenic parietal lobe. Among extrafrontal patients, only one patient showed delayed responses in the frontal lobe.

In 9 of the 11 patients with delayed responses in the frontal lobes, the areas stimulated to induce delayed responses and the areas showing delayed responses were adjacent. In one patient, stimulation of the lateral frontal cortex induced delayed responses in medial frontal cortex. In the remaining patient, delayed responses were seen in the orbitofrontal cortex when different areas of the frontal cortex, including the orbitofrontal cortex, were stimulated (see table 1). In all 11 frontal patients with frontal delayed responses, the cortical regions showing seizure onset, the areas showing frontal delayed responses, and the areas stimulated to induce frontal delayed responses were in the same frontal lobe (the epileptogenic frontal lobe). In 7 of the 11 patients with frontal delayed responses, the frontal regions showing seizure onset were similar to the areas stimulated to induce delayed responses and to the areas showing delayed responses. This suggests that in the frontal lobe, the relation between seizure onset and areas showing delayed responses is high but not as close as previously reported in the temporal lobes,[7] possibly owing to the fact that seizure onset tends to be less focal in frontal than in temporal lobes.

Repetitive responses. These consisted of two or more consecutive waves, each resembling the initial early response (figures 4 and 5). Thus, they appeared as a burst of high-amplitude slow waves starting immediately after the stimulus, often with superimposed smaller sharp (spike) components. As with delayed responses, repetitive responses were not always seen after every identical stimulus, with occurrence rates between 50 and 90%. In contrast to delayed responses, repetitive responses to identical stimulation showed similar latency from the stimulus and were usually different from the ongoing spontaneous interictal activity. To our knowledge, repetitive responses have not been previously described. We have observed them exclusively when stimulating the frontal lobes in 10 frontal patients. In five patients, repetitive responses showed widespread and bilateral distribution, involving most recording channels (see figure 4). In the remaining five patients, repetitive responses showed a regional distribution,

Table 1 *Responses to SPES, pathology, and outcome in frontal patients*

Patient no.	Location of SPES to induce DR	Location of DR	Location of SPES to induce RR	Surgery	Pathology	Outcome	Follow-up, mo
1	Lat-med-orb frontal	Orb frontal	Bifrontal	No	NA	NA	NA
2	Lat frontal	Lat frontal/ temp	No RR	Yes	FCD lat frontal	1	14
3	No DR	No DR	Med frontal	Yes	FCD med frontal	1	28
4	No DR	No DR	Med frontal	No	NA	NA	NA
5	Lat frontal	Lat frontal	No RR	Yes	Perinatal scar lat frontal	3	15
6	Lat frontal	Med frontal	No RR	Yes	FCD frontal	3	13
7	No DR	No DR	Med frontal	No	NA	NA	NA
8	No DR	No DR	Bifrontal	No	NA	NA	NA
9	Lat frontal	Lat frontal	Lat frontal	No	NA	NA	NA
10	Med frontal	Med frontal	No RR	Yes	FCD med/lat frontal	4	20
11	No DR	No DR	Med frontal	Yes	FCD med frontal	2	49
12	Lat frontal	Lat frontal	Lat frontal	Yes	DNT lat frontal	2	27
13	Lat frontal	Lat frontal	Lat frontal	No	NA	NA	NA
14	Lat-med frontal	Lat-med frontal	Bifrontal	No	NA	NA	NA
15	Med frontal	Med frontal	No RR	Yes	Nonspecific	3	14
16	No DR	No DR	No RR	Yes	FCD lat frontal	3	12
17	Med frontal	Med frontal	No RR	Yes	NA (CHH)	3	22

SPES = single-pulse electrical stimulation; DR = delayed responses: RR = repetitive responses; FCD = focal cortical dysplasia Taylor type; DNT = dysembryoplastic neuroepithelial tumor; CHH = coagulation of hypothalamic hamartoma; lat = lateral; med = medial; orb = orbital; NA = not applicable; temp = temporal.

involving more than three subdural electrodes from a mat or strip or electrodes from more than one intracerebral electrode bundle (see figure 5). Among the 10 patients with repetitive responses, 7 showed them exclusively when the epileptogenic frontal lobe was stimulated, even if repetitive responses were recorded bilaterally as a response to unilateral stimulation. The remaining three patients showed repetitive responses on stimulation of either frontal lobe. Therefore, we have considered that areas whose stimulation elicited repetitive responses are functionally abnormal, regardless of the distribution of repetitive responses. Their locations are shown in table 1. Repetitive responses were seen neither in extrafrontal patients nor in frontal patients when stimulating outside frontal lobes.

As a consequence of our previous[7] and the current results, we suspect that the abnormal areas tend to be those where delayed responses were recorded and those stimulated when repetitive or delayed responses were seen. Therefore, to simplify wording throughout the text, the areas where delayed responses were recorded and the areas whose stimulation evoked repetitive or delayed responses will be called abnormal SPES areas.

Localizing value of SPES in frontal lobe epilepsy. To estimate the value of SPES to identify frontal epileptogenicity, we have compared the proportion of frontal and extrafrontal patients showing frontal late responses. Sixteen of the 17 frontal patients showed some abnormal SPES areas in the frontal lobes. Among these 16 frontal patients, 6 had delayed responses, 5 had repetitive responses, and 5 had both delayed and repetitive responses in the frontal lobes. Therefore, all frontal patients except one had late responses when at least one frontal lobe was stimulated. In contrast, none of the 13 extrafrontal patients had frontal repetitive responses, and only 1 had frontal delayed responses. The latter patient had frontal and temporal delayed responses. The proportion of patients showing frontal late responses was higher among frontal than among extrafrontal patients (table 2; $p < 0.001$, Fisher exact test). The sensitivity of SPES to localize the epileptogenic frontal lobe in our series was 94% (16/17), the specificity was 92% (12/13), the positive predictive value was 94% (16/17), and the negative predictive value was 92% (12/13).

Lateralizing value of SPES in frontal lobe epilepsy. To estimate the value of SPES to lateralize the epileptogenic frontal lobe, we have compared the proportion of patients showing delayed or repetitive responses when stimulating their epileptogenic vs their nonepileptogenic frontal lobes. Fourteen frontal patients had electrodes located in both frontal lobes. Among the 14 patients, 1 did not have late responses, 10 had late responses exclusively when stimulating the epileptogenic lobe, and 3 had repetitive responses when stimulating either frontal lobe. Therefore, of the 14 frontal patients with bilateral frontal electrodes, 13 had late responses (delayed or repetitive) when stimulating the epileptogenic frontal lobe, whereas only 3 showed late responses (repetitive) when stimulating the nonepileptogenic lobe ($p < 0.001$; Fisher exact test). In this series, the sensitivity of SPES to lateralize the epileptogenic frontal lobe was 93% (13/14), the specificity was 79% (11/14), the positive predictive value was 81% (13/16) and the negative predictive value 92% (11/12).

Relation between SPES and neuropathologic findings. Ten of the 17 frontal patients had surgery for the treat-

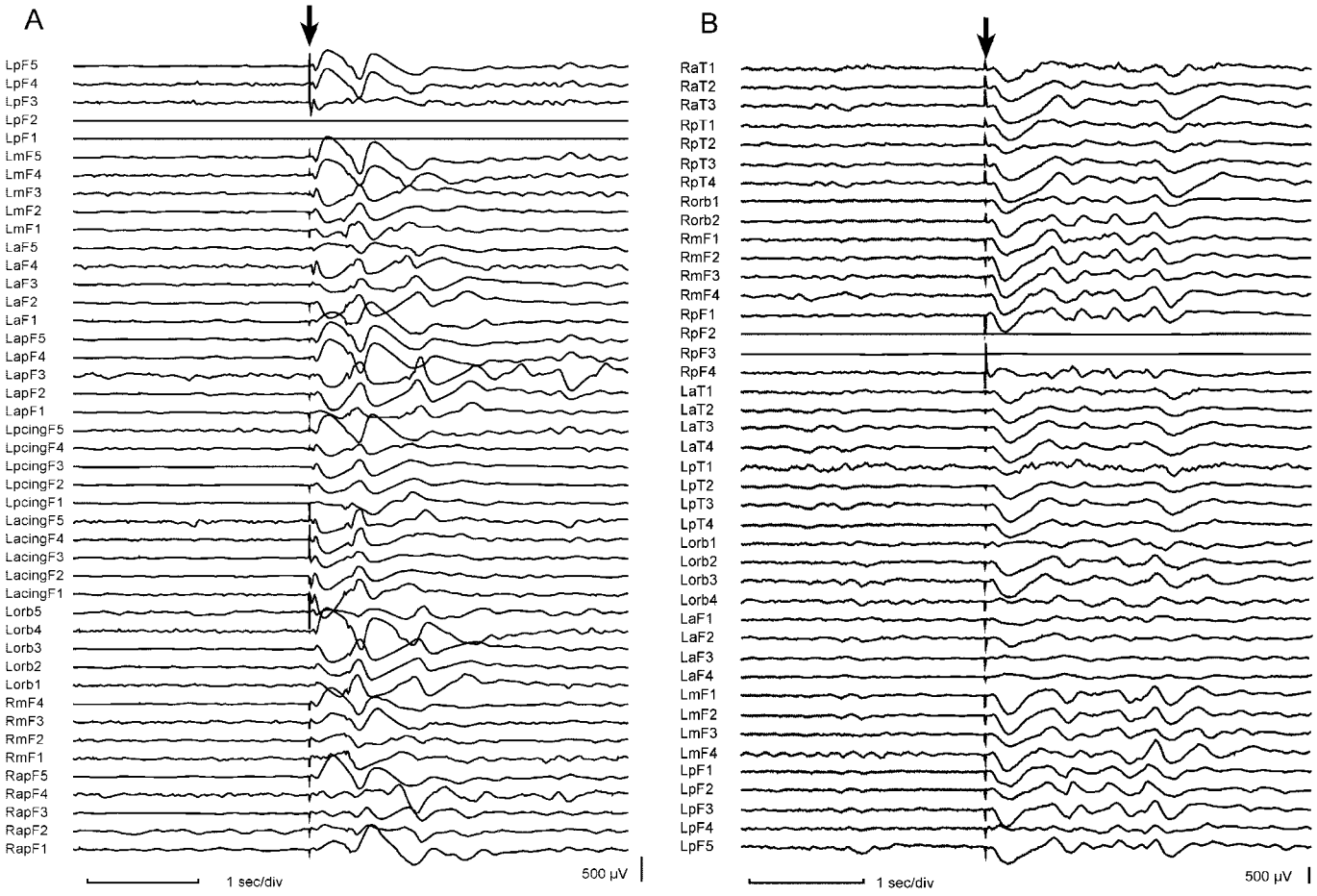

Figure 4. Widespread repetitive responses evoked by single-pulse electrical stimulation in the frontal lobe. (A) Bilateral repetitive responses with similar morphology and distribution to the first early response (Patient 11). Stimulation was performed through electrodes 1 and 2 of the left posterior frontal electrode bundle (LpF1 and 2). Recordings have been displayed in common average reference. (B) Bilateral repetitive responses with similar distribution but lower amplitude than the first early response (Patient 8). Stimulation was performed through electrodes 2 and 3 of the right posterior frontal electrode bundle (RpF 2 and 3). Recordings have been displayed in common reference to Pz. Both recordings have similar time calibration but different gain. Both patients had intracerebral (depth) electrodes. Electrode positions and labels are as shown in figure 1B.

ment of their epilepsy (see table 1). Nine patients had frontal resections, and one had a coagulation of a hypothalamic hamartoma. Among the nine frontal resections, six showed Taylor-type focal cortical dysplasia (FCD), characterized by disorganized cortical lamination, large abnormal neurons, and cells with abundant pale glassy cytoplasm (balloon cells). In five of the six patients with FCD, the lesion involved one or more resection margins, suggesting that the lesion extended to or beyond the limits of the resection. Among the patients with abnormalities other than FCD, one showed a scar with ulegyria, suggestive of perinatal ischemic injury. One patient showed a heavily calcified dysembryoplastic neuroepithelial tumor composed of a solitary nodule in which small oligodendroglia-like cells, astrocytes, and mature neurons were identified. One patient showed only mild nonspecific changes: subpial fibrillary gliosis, mild inflammatory infiltrate in the leptomeninges probably related to previously used subdural electrodes, and a small depth electrode track with a very mild foreign body granulomatous reaction. Seven of the eight patients with frontal resections had specific structural abnormalities in the abnormal SPES areas.

Relation between SPES and postsurgical seizure outcome. All 10 operated frontal patients have a follow-up period longer than 12 months (mean follow-up = 22 months). Among these 10 patients, the 4 patients who had a complete resection of areas responsible for frontal late responses enjoyed a favorable outcome. One of these four patients showed additional delayed responses in the temporal lobe. In the remaining six patients, it was not possible to remove all areas showing delayed responses, and all six experienced poor seizure outcome. Among these six patients with poor seizure outcome, one showed several regions with delayed responses, of which one was a functionally relevant area (speech) that was not removed. This patient had a 95% reduction in seizures but still has at least one seizure per week (Engel grade III). Among the remaining five patients, three had delayed responses exclusively outside the operated area and had poor outcome (Engel grades III or IV). One patient did not have late responses in the frontal lobes and had an Engel grade III outcome. The last patient with delayed responses in the frontal lobe and poor outcome had a subthalamic hamartoma that was thermocoagulated without frontal surgery.

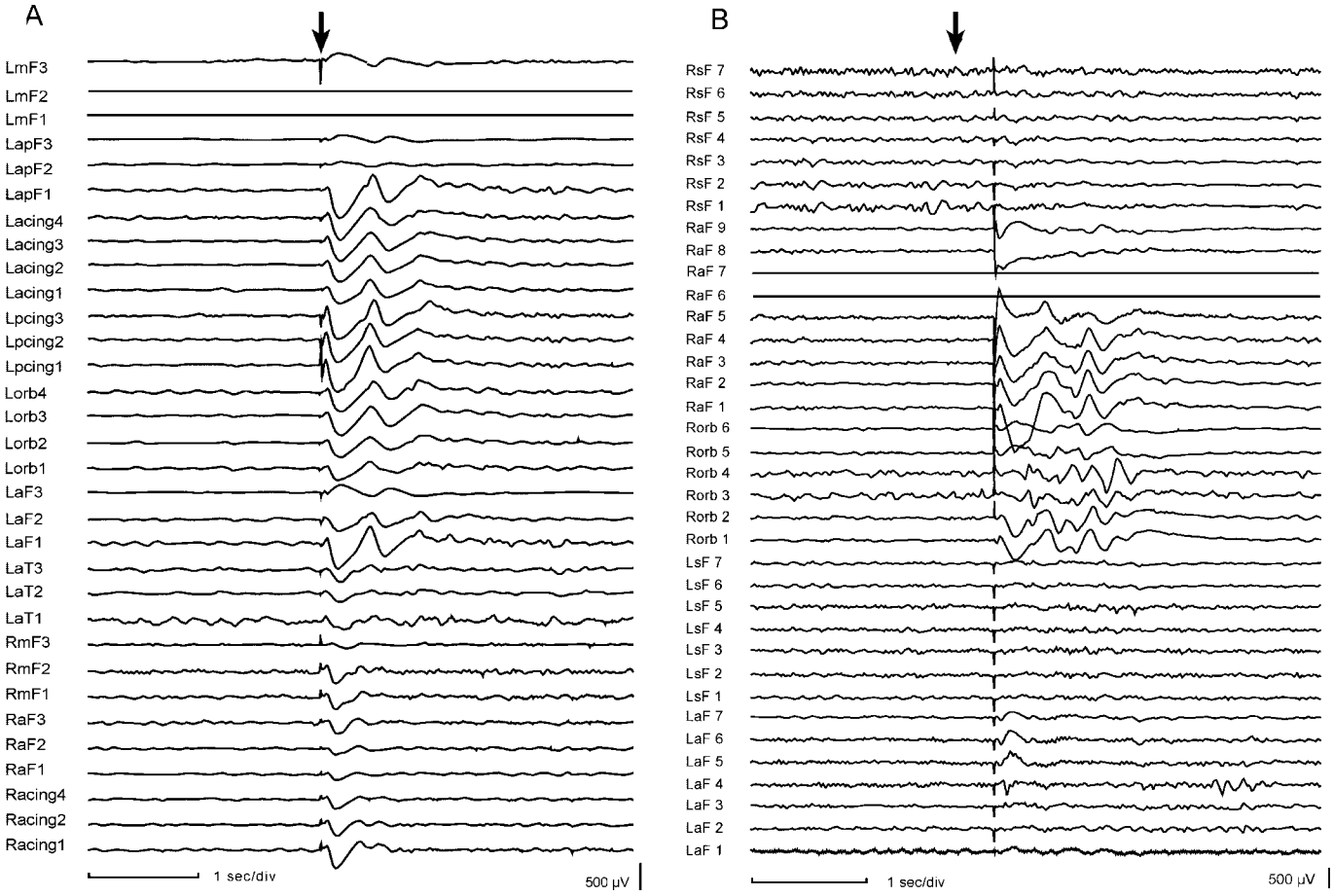

Figure 5. Regional repetitive responses evoked by single-pulse electrical stimulation of the frontal lobe. (A) Repetitive responses restricted to one hemisphere (Patient 3). Stimulation was performed through electrodes 1 and 2 of the left midfrontal electrode bundle (LmF1 and 2). Recordings have been displayed in common reference to Pz. (B) Repetitive responses restricted to the anterior and cortex in Patient 1. Stimulation was performed through electrodes 6 and 7 of the right anterior frontal electrode bundle (RaF 6 and 7). Recordings have been displayed in common reference to Pz. Both patients had intracerebral (depth) electrodes. Electrode positions and labels are as shown in figure 1B.

This patient had two seizure types before surgery, of which only one was abolished by surgery (Engel grade III). In conclusion, there was a relation between favorable seizure outcome and complete removal of abnormal SPES areas in the frontal cortex (table 3; $p < 0.005$).

It is important to note that in five of the six patients with poor outcome, surgery would not have been carried out or the procedure would have been modified if only SPES findings had been considered. On the other hand, SPES findings would have reinforced but not modified the surgical decision in the four patients with favorable outcome, as resections included all abnormal SPES areas.

Table 2 *Localizing value of DR/RR in the frontal lobe*

	Frontal patients	Extrafrontal patients	Total
Frontal DR/RR	16	1	17
No frontal DR/RR	1	12	13
Total	17	13	30

$p < 0.001$ (Fisher exact test).

DR = delayed responses; RR = repetitive responses.

Discussion. The aim of this study was to evaluate SPES as a tool to identify epileptogenic cortex in patients with frontal lobe epilepsy. We have seen three types of cortical responses to SPES: early, delayed, and repetitive responses. Delayed and repetitive responses

Table 3 *Relation between DR/RR and postsurgical seizure outcome in frontal patients (follow-up > 12 months)*

	Favorable outcome, (Engel's I or II)	Poor outcome, (Engel's III or IV)	Total
Frontal DR/RR area completely resected	4	0	4
No frontal DR/RR or frontal DR/RR in non-resected areas	0	6	6
Total	4	6	10

$p < 0.005$ (Fisher exact test).

DR = delayed responses; RR = repetitive responses.

are classified as late responses, as they occurred after the early response. Early responses to SPES were seen when stimulating at most sites in all patients, suggesting that they are normal responses of the cortex to SPES.[7] Such responses appear to be equivalent to those described by other authors using similar stimulation parameters.[7,12-16] Delayed responses arising from the frontal lobe were seen in 11 frontal patients and had electrophysiologic characteristics similar to those previously described by ourselves[7] and to those anecdotally described in the frontal lobe when studying transcallosal frontal responses.[15] In addition, we describe here a new type of cortical responses to SPES, the repetitive responses, which were generated only when stimulating the frontal lobes of patients with frontal lobe epilepsy and were recorded over more widespread areas than delayed responses, sometimes involving both hemispheres. We presume that late responses are equivalent to the "after-discharges" often seen when stimulating with trains of electrical pulses. We have chosen the term "late responses" to stress that they are elicited by different methodology and to distinguish them from the normal "early responses," which are not visible when trains of pulses are used.

Because of the high proportion of regional seizure onsets in frontal patients, it was difficult to correlate seizure onset with abnormal SPES areas, which were generally more localized. Therefore, in the current work, we have restricted the analysis to lobe identification. To establish the association between epileptogenic frontal cortex and late responses, we have carried out three types of comparisons: 1) an intrapatient comparison between responses from epileptogenic and nonepileptogenic frontal lobes in frontal patients, 2) an interpatient comparison between frontal responses in frontal patients and in extrafrontal patients, and 3) comparison of neuropathologic findings and surgical outcome among frontal patients who had complete or incomplete resection of abnormal SPES regions.

With regard to intrapatient comparisons, whereas 93% (13/14) of frontal patients had late responses when areas of their epileptogenic frontal lobe were stimulated, only 21% (3/14) also had repetitive responses to stimulation of their nonepileptogenic frontal lobes. With regard to interpatient comparisons, 94% (16/17) of frontal patients showed late frontal responses to SPES. None of the 13 extrafrontal patients showed repetitive responses when their frontal lobes were stimulated and only 1 extrafrontal patient showed delayed responses in the frontal lobe. Therefore, the presence of frontal late responses was associated with frontal lobe epileptogenicity ($p < 0.001$, Fisher exact test) with a high sensitivity and specificity. In addition, repetitive responses appear to occur specifically as a response to stimulation of the frontal lobe(s).

An important finding is that operated patients showed structural abnormalities demonstrated by neuropathology in the abnormal SPES areas. This means that frontal delayed and repetitive responses arose from structurally abnormal regions, which showed mainly cortical dysplasia in the current series. In addition, there was an association between surgical outcome and complete removal of abnormal SPES areas in the frontal cortex ($p < 0.005$, Fisher exact test). This finding further suggests that delayed and repetitive responses arise from functionally abnormal regions. This is not surprising, as abnormal responses to SPES are probably related to changes in cortical excitability and can therefore identify potentially epileptogenic areas. The findings suggest that surgery should aim at removing areas where delayed responses are seen and areas whose stimulation elicited repetitive responses. This is of paramount clinical relevance as SPES appears to provide additional evidence of epileptogenicity and appears to be a good predictor of pathology and surgical outcome. Indeed, the absence of late responses might suggest that the electrodes are not located close to epileptogenic cortex.

A problem commonly encountered when interpreting intracranial recordings in frontal lobe epilepsy is that seizure onset is sometimes detected by many electrodes simultaneously (regional or diffuse onset). Such a widespread seizure onset may be due to the existence of a large epileptogenic zone or to rapid propagation of ictal activity from a more discrete seizure onset located distant from any recording electrode. Each of these interpretations has distinctly different clinical implications, and SPES can help in distinguishing between them. The existence of late responses related to the area of seizure onset would imply that this area is epileptogenic and that its removal would increase the likelihood of seizure control after surgery. In contrast, the absence of late responses suggests that seizures arise from remote areas, and the patient may not benefit from surgery in the recording areas.

Two different pathophysiologic mechanisms could be the basis of repetitive and delayed responses. Repetitive responses seem to be induced when the epileptogenic area is stimulated and consist of the repetition of the initial normal early response. Therefore, repetitive responses may arise from the immediate activation of a cortical (or thalamocortical) loop in the stimulated cortex, which triggers a re-entry of neuronal activity, resulting in repetition of the initial response. The fact that repetitive responses were widespread (sometimes bilateral) but induced by focal stimulation of one frontal lobe might be explained by a corticosubcortical loop. This is further supported by the finding that subcortical structures appear to have more connections with frontal than temporal cortices.[17] We hypothesize that in normal cortex, the mechanisms responsible for repetitive responses do not exist or are suppressed by inhibition. Delayed responses are more difficult to explain owing to their long and variable delay (100 milliseconds to 1 second). As delayed responses are seen in areas involved at seizure onset and their morphology resembles that of interictal discharges,

they could be explained by the presence of a cortical loop in the epileptogenic cortex lasting for some hundreds of milliseconds.[7] This loop would be activated by afferents from the stimulated cortex, allowing for a build-up of activity or recruitment of neurons until an epileptiform discharge is triggered. The efficacy of such neuronal recruitment would depend on neuronal or glial mechanisms that determine excitability of the epileptogenic region. Thus, both delayed and repetitive responses could be due to an abnormal control of cortical activity, probably due to an altered balance between excitation and inhibition. A finding that supports this hypothesis is that responses to SPES resembling repetitive and delayed responses have been seen in animal models with altered balance between excitation and inhibition, such as in vitro experiments with disinhibited neocortical slices,[18] in hippocampal slices exposed to Mg^{2+}-free medium,[19] and after local injection of tetanus toxin.[20,21]

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References

1. Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain. Boston: Brown, 1954.*
2. Rasmussen T. Tailoring of cortical excisions for frontal lobe epilepsy. Can J Neurol Sci 1991;18(suppl):606–610.
3. Ferrier CH, Engelsman J, Alarcon G, Binnie CD, Polkey CE. Prognostic factors in presurgical assessment of frontal lobe epilepsy. J Neurol Neurosurg Psychiatry 1999;66:350–356.
4. Mosewich RK, So EL, O'Brien TJ, et al. Factors predictive of the outcome of frontal lobe epilepsy surgery. Epilepsia. 2000;41:843–849.
5. Williamson PD. Frontal lobe seizures. Problems of diagnosis and classification. Adv Neurol 1992;57:289–309.
6. Quesney LF, Constain M, Rasmussen T, Olivier A, Palmini A. Presurgical EEG investigation in frontal lobe epilepsy. Epilepsy Res [Suppl] 1992;5:55–69.
7. Valentin A, Anderson M, Alarcon G, et al. Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo. Brain 2002;125:1709–1718.
8. Elwes RDC .*Invasive neurophysiological evaluation. In: Oxbury J, Polkey CE, Duchowny M, eds. Intractable focal epilepsy. London: Saunders, 2000:595–615.*
9. Alarcon G, Binnie CD, Elwes RD, Polkey CE. Power spectrum and intracranial EEG patterns at seizure onset in partial epilepsy. Electroencephalogr Clin Neurophysiol 1995 94:326–337.
10. Selway R, Polkey CE, Mullatti N. Percutaneous thermocoagulation of hypothalamic hamartomas: safety and beneficial effect on seizures. Epilepsia 2002;43:351. Abstract.
11. Engel Jr., J Van Ness P, Rasmussen T, Ojemann GA. *Outcome in respect to epileptic seizures. In: Engel J Jr, ed. Surgical treatment of the epilepsies. New York: Raven Press, 1993:609–621.*
12. Wilson CL, Isokawa M, Babb TL, Crandall PH. Functional connections in the human temporal lobe. I. Analysis of limbic system pathways using neuronal responses evoked by electrical stimulation. Exp Brain Res 1990;82:279–292.
13. Rutecki PA, Grossman RG, Armstrong D, Irish-Loewen S. Electrophysiological connections between the hippocampus and entorhinal cortex in patients with complex partial seizures. J Neurosurg 1989 May;70(5): 667–675.
14. Brazier M. Evoked responses recorded from the depths of the human brain. Ann NY Acad Sci 1964;112:33–35.
15. Buser P, Bancaud J, Chauvel P. Callosal transfer between mesial frontal areas in frontal lobe epilepsies. Adv Neurol 1992;57:589–604.
16. Buser P, Bancaud J. Unilateral connections between amygdala and hippocampus in man. A study of epileptic patients with depth electrodes. Electroencephalogr Clin Neurophysiol. 1983 Jan;55:1–12.
17. Velasco M, Velasco F, Velasco AL, et al. Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. Arch Med Res 2000 May;31:304–315.
18. Chagnac-Amitai Y, Connors BW. Synchronized excitation and inhibition driven by intrinsically bursting neurons in neocortex. J Neurophysiol 1989;62:1149–1162.
19. Kohling R, Vreugdenhil M, Bracci E, Jefferys JG. Ictal epileptiform activity is facilitated by hippocampal GABAA receptor-mediated oscillations. J Neurosci 2000;20:6820–6829.
20. Jefferys JG. Chronic epileptic foci in vitro in hippocampal slices from rats with the tetanus toxin epileptic syndrome. J Neurophysiol 1989;62: 458–468.
21. Empson RM, Amitai Y, Jefferys JG, Gutnick MJ. Injection of tetanus toxin into the neocortex elicits persistent epileptiform activity but only transient impairment of GABA release. Neuroscience 1993 57:235–239.