Deep Brain Stimulation in Patients with Refractory Temporal Lobe Epilepsy

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Summary: Purpose: This pilot study prospectively evaluated the efficacy of long-term deep brain stimulation (DBS) in medial temporal lobe (MTL) structures in patients with MTL epilepsy.

Methods: Twelve consecutive patients with refractory MTL epilepsy were included in this study. The protocol included invasive video-EEG monitoring for ictal-onset localization and evaluation for subsequent stimulation of the ictal-onset zone. Side effects and changes in seizure frequency were carefully monitored.

Results: Ten of 12 patients underwent long-term MTL DBS. Two of 12 patients underwent selective amygdalohippocampectomy. After mean follow-up of 31 months (range, 12–52 months), one of 10 stimulated patients are seizure free (>1 year), one of 10 patients had a >90% reduction in seizure frequency; five of 10 patients had a seizure-frequency reduction of ≥50%; two of 10 patients had a seizure-frequency reduction of 30–49%; and one of 10 patients was a nonresponder. None of the patients reported side effects. In one patient, MRI showed asymptomatic intracranial hemorrhages along the trajectory of the DBS electrodes. None of the patients showed changes in clinical neurological testing. Patients who underwent selective amygdalohippocampectomy are seizure-free (>1 year), AEDs are unchanged, and no side effects have occurred.

Conclusions: This open pilot study demonstrates the potential efficacy of long-term DBS in MTL structures that should now be further confirmed by multicenter randomized controlled trials. Key Words: Refractory epilepsy—Neurostimulation—Deep brain stimulation—Temporal lobe.

Epilepsy is the second most common chronic neurologic disease after cerebrovascular disorders, affecting 0.5–1% of the population (Hauser et al., 1993). More than 30% of all epilepsy patients have uncontrolled seizures or unacceptable medication-related side effects despite adequate pharmacologic treatment (Kwan and Brodie, 2000). Refractory epilepsy increases the risk of cognitive deterioration and psychosocial dysfunction and is associated with excess injury and mortality (Brodie and Dichter, 1996). Therapeutic options that can be offered to patients with refractory epilepsy include trials with newly developed antiepileptic drugs (AEDs), resulting in seizure freedom in ~7% of these patients (Fisher, 1993). Epilepsy surgery is another option that leads to long-term seizure freedom in an average of 58% of the patients, depending on the localization of the seizure focus (Engel et al., 2003; Lee et al., 2005). For the remainder of patients, few options are left. Neurostimulation, defined as direct administration of electrical pulses to nervous tissue to modulate a pathologic substrate and to achieve a therapeutic effect may be such an alternative. Which part of the nervous system is being targeted and how the stimulation is being administered may be variable. Vagus nerve stimulation (VNS) is an extracranial form of stimulation that was developed in the 1980s and is now routinely available in epilepsy centers worldwide (Ben Menachem, 2002). Deep brain stimulation (DBS) has previously been used for movement disorders and pain (Nguyen et al., 2000; Pollak et al., 2002; Volkman et al., 2004). Moreover, several new indications such as obsessive–compulsive behavior and different headache syndromes are being investigated with promising results (Nuttin et al., 1990; Leone et al., 2003, 2005). In the past, DBS of various targets such as...
the cerebellum, the locus coeruleus, and the thalamus was performed in patients with spasticity or psychiatric disorders who also had epilepsy, but the technique was not fully explored or developed into an efficacious treatment option for patients with epilepsy (Cooper, 1978; Wright et al., 1984; Upton et al., 1985; Feinstein et al., 1989). The vast progress in biotechnology along with the experience in other neurologic diseases in the past decade, has led to a renewed interest in DBS for epilepsy. A few epilepsy centers worldwide have recently initiated trials with DBS in different intracerebral structures such as the thalamus, the subthalamic nucleus, the caudate nucleus, and the cerebellum (Fisher et al., 1992; Velasco et al., 1995; Chkhenkeli and Chkhenkeli, 1992; Chabardes et al., 2002; Hodaie et al., 2002; Velasco et al., 2005). Two major stimulation strategies can be pursued.

One approach is to target crucial central nervous system structures that are considered to have a “pacemaker,” “triggering,” or “gating” role in the epileptogenic network, such as the thalamus or the subthalamic nucleus (Iadarole and Gale, 1982). At Ghent University Hospital, the approach chosen was to evaluate potential interference with the ictal-onset zone. In medial temporal lobe (MTL) epilepsy, the epileptogenic region is believed to be in the medial temporal lobe, as documented by the gold-standard investigation using intracranial electrodes (King and Spencer, 1995). It is also supported by the high number of seizure-free patients after resection of this region (Engel, 1993). On the one hand, investigating the potential efficacy of DBS in patients with MTL epilepsy is inspired by the search for less-invasive procedures compared with tissue resection. On the other hand, it fits in the search for alternative treatments for unsuitable candidates for resective surgery, such as patients with bilateral MTL epilepsy.

Patients scheduled for invasive recordings because of discrepant findings on noninvasive presurgical evaluation must undergo an implantation procedure and were considered to represent ideal candidates for the evaluation of MTL DBS that can be performed by using the electrodes implanted for diagnostic reasons.

Preliminary findings in three patients studied in our group were reported previously (Vonck et al., 2002).

PATIENTS AND METHODS

Patient selection

The study protocol and the informed-consent documents were approved by the Ethics Committee of Ghent University Hospital. Patients with refractory epilepsy were enrolled in a presurgical evaluation protocol at the Reference Center for Refractory Epilepsy at Ghent University Hospital, a tertiary neurological referral center in Belgium. The presurgical protocol was published previously and includes video-EEG monitoring, optimum 1.5- or 3-T magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography, and comprehensive neuropsychological assessment, according to international standards (EFNS task force, 2000). Twelve patients with medically refractory epilepsy were included in the study (Fig. 1). Inclusion criteria consisted of (a) suspicion of temporal lobe epilepsy on the basis of video-EEG monitoring; (b) seizure frequency of at least one complex partial seizure (CPS) per month, confirmed during a prospective preintervention baseline period of 6 months; and (c) requirement for invasive video-EEG monitoring in the bilateral MTL area and other subdural brain areas because of incongruent findings during noninvasive presurgical evaluations to localize the seizure onset. During the preintervention baseline period, all patients were receiving a stable combination therapy of two or more AEDs.

Surgical procedure

During an MRI-guided stereotactic procedure under general anesthesia, two quadripolar DBS electrodes (model 3387; Medtronic, Fridley, MN, U.S.A.) were implanted in each hemisphere through two parietooccipital burrholes. Details of this procedure in our center were published previously (Vonck et al., 2002). The most anterior electrode on each side was placed in the amygdala. The second electrode was placed in the anterior part of the hippocampus on each side. The trajectory of the second electrode had a small angle with the first one. Each electrode has four cylindrical electrode contacts of 1-mm diameter, 1.5-mm length, and an intercontact distance of 1.5 mm. On each electrode, the four electrode contacts cover a total length of 10.5 mm. In all patients, additional subdural grids and/or strips in various combinations were placed on the temporal and/or frontal neocortex, depending on the results of the presurgical evaluation during a procedure under general anesthesia. Patients were allowed to recover in the neurosurgical unit for a period of 48 h. Subsequently all intracranial electrode contacts and 27 scalp-EEG electrodes were connected with the video-EEG monitoring system (128-channel digital video-EEG, Beehive; Astromed-Grass-Telefactor, West Warwick, RI, U.S.A.). The precise location of the intracranial electrode contacts was assessed by performing MRI by using an MPRAGE sequence.

Recording and stimulation paradigm

After 48 h of video-EEG monitoring, during which AEDs remained unchanged, AEDs were gradually tapered until habitual seizures were recorded (AED tapering condition). The finding of a unilateral or bilateral focal or regional MTL ictal onset was the criterion for offering patients the choice to undergo continuous MTL DBS. Patients with unilateral MTL seizure onset were stimulated by using the ipsilateral amygdalar and hippocampal DBS electrodes. In patients with bilateral MTL onset, bilateral hippocampal stimulation was performed.
Initial DBS was performed by using a temporary external pulse generator (DualScreen 3628; Medtronic) during a trial period (acute stimulation condition) before implanting patients with an internalized pulse generator. At any time during the study, patients could make the choice of interrupting the ongoing stimulation treatment and undergoing resective surgery, when indicated. Immediately before the acute stimulation condition, subdural grids and strips were removed. The aim was to keep patients on the tapered AED regimen. In case of an acute increase in seizure frequency, reinstallation of AEDs at the baseline dosage and/or administration of escape medication was planned. To determine the output voltage level for initiating DBS, we connected the hippocampal electrode to the EEG recording system, whereas the amygdalar electrode was set to 130 Hz, and pulse width, to 450 µs, based on earlier experience with DBS in the medial temporal lobe by Velasco et al. (2001). Pairs of adjacent electrode contacts on both DBS electrodes were continuously stimulated in a bipolar way with the most anterior electrode contact and the third electrode contact serving as cathodes. Individual pulses consisted of biphasic square-wave Lilly pulses.

For patients with unilateral MTL seizure onset, this action was performed ipsilateral to the side of seizure onset. In patients with bilateral MTL seizure onset, this action was performed bilaterally only for the hippocampal DBS electrodes.

To obtain an objective and comparable efficacy parameter during the acute stimulation condition, interictal spike activity in the stimulated area was evaluated. The criterion for implantation of a pulse generator (Kineta, Medtronic) and entering the chronic stimulation condition was the finding of a reduction of interictal spikes in the stimulated area of >50% during 7 consecutive days in the acute stimulation condition compared with the AED-tapering condition. The rationale for comparing spike counts during the AED-tapering condition and the acute stimulation condition was that the initiation of stimulation was the only intervention that differentiated these two conditions from each other. DBS was interrupted every morning at about the same time for a 1-h period during quiet wakefulness, typically from 10 am to 11 am. The DBS electrodes were reconnected with the video-EEG monitoring equipment for recording of EEG activity in the stimulated area during the remaining 23 h of the day. Epileptiform discharges were visually identified and manually counted during four consecutive intervals of 15 min/day. The period of spike counting was ≥6 hours remote from the occurrence of seizures. To assess acute side effects, clinical neurologic examination and bedside neuropsychological testing (including reading, naming, and memory testing) were performed daily during the acute stimulation condition. Formal neuropsychological assessment was planned after 12 months in all patients. A detailed account of neuropsychological outcome data is the object of a separate study.

When a >50% reduction of interictal spikes was not achieved within 21 days, the study protocol allowed a prolonged acute-stimulation condition. This consisted of a trial with an adjusted stimulation frequency of 200 Hz. When, after a prolonged acute-stimulation phase of another 3 weeks, a >50% reduction of interictal spikes was not achieved during 7 consecutive days, patients were offered resective surgery when indicated or a continuation of best medical therapy.

When patients entered the prolonged-stimulation condition, the implantable pulse generator was placed in an abdominal subcutaneous pouch. The Kinerta device was connected to two DBS electrodes through two extension wires. This required a short surgical procedure under general anesthesia. After this surgical procedure, patients were followed up in the epilepsy clinic at regular 2-week intervals. Similar to the short-term stimulation condition, the aim was to keep patients on the tapered-AED regimen throughout the prolonged-stimulation condition. In case of an acute increase in seizure frequency, reinstallation of AEDs at the baseline dosage and/or administration of escape medication was allowed.

After 12 months of long-term DBS, the AED regimen could be changed according to best medical practice. Gradual increase of stimulation output current in patients who were not seizure free was allowed.

Data analysis

The present study is a comparative pre–post test, prospective, open pilot trial of efficacy and safety of unilateral DBS in the MTL. During the entire study period from the prospective 6 month preintervention baseline period over the prospective AED tapering condition and short-term stimulation condition to the prolonged-stimulation condition, seizure frequency, adverse events, and concomitant AED use were carefully monitored by using a seizure diary. Mean spike counts per hour during the short-term stimulation condition were compared with mean spike counts per hour during the entire AED-tapering condition. Frequency of CPS ± secondary generalization
(SG) during the prolonged-stimulation condition was compared with the mean monthly frequency of such seizures during 6 months before DBS. Postintervention seizure outcome was assessed during the last 6 months of follow-up and categorized into the following groups: seizure-free; >90% seizure reduction; ≥50% seizure reduction; 30–49% seizure reduction; and <30% seizure reduction (nonresponder).

RESULTS

All patients included in this study were candidates for invasive EEG recording because of the absence of any structural abnormalities and/or incongruent results in the noninvasive presurgical evaluation. Table 1 shows the patients’ individual neuroimaging results. In eight of 12 patients, optimal MRI showed no structural abnormalities; in two patients, unilateral MTL signal abnormalities and some degree of atrophy were found; in one patient, MTL atrophy was associated with anterior temporal and neocortical temporal gliosis; and in one patient, bilateral subcortical white matter lesions in the parietal lobe were found.

The stereotactic implantation procedure of DBS electrodes was uneventful in 11 of 12 patients. In patient 11, asymptomatic hemorrhages occurred along the trajectory of the depth electrodes. This bleeding was discovered when a routine MRI was performed for postoperative localization of the invasive electrodes. Postoperative MRI imaging for electrode localization confirmed localization of one DBS electrode in the amygdala and one DBS electrode in the anterior hippocampus in each hemisphere (Fig. 2).

Table 1 describes invasive video-EEG monitoring results. In all patients, unilateral or bilateral interictal spikes were recorded from the MTL electrodes. Focal EEG ictal onset, involving one or more electrode contacts on a single DBS electrode, was identified in six of 12 patients, typically consisting of a low-voltage, high-frequency discharge in the hippocampal electrode contacts on one side, occurring seconds before clinical seizure onset and followed by spread to ipsilateral neocortical areas and the contralateral MTL structures. In five of 12 patients, intracranial ictal EEG onset was “regional,” referring to a more widespread distribution of early changes involving more electrode contacts on different electrodes. The regional ictal onset was unilateral in all patients, but in patient 4, spreading to the contralateral medial structures occurred within a few seconds. In one patient, bilateral MTL onset was found, with five seizures originating from the left temporal lobe and one from the right temporal lobe.

Subsequently, 11 of 12 patients entered the acute-stimulation condition. One patient with unilateral right focal ictal onset chose to undergo resective surgery immediately. During the acute stimulation condition, continuous bipolar 130-Hz stimulation ipsilateral to the ictal onset was delivered to the amygdalar and hippocampal electrode contacts in 10 of 11 patients. The patient with bilateral independent seizure onset was stimulated bilaterally with the same stimulation parameters in the hippocampus. Ten of

<table>
<thead>
<tr>
<th>TABLE 1. Results of neuroimaging, invasive video-EEG monitoring, and consequent therapeutic intervention</th>
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<tbody>
<tr>
<td>Patient number</td>
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</tr>
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<td>1</td>
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<td>11</td>
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<td>12</td>
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</tbody>
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MRI, magnetic resonance imaging; L, left; T, temporal; AH, amygdalohippocampal; R, right; SAH, selective amygdalohippocampectomy; TL, temporal lobectomy; HS, hippocampal sclerosis; B, bilateral; P, parietal; WML, white matter lesions.
11 patients showed a >50% reduction in interictal spikes in 1-h recording sessions on 7 consecutive days. In patient 7, interictal spike frequency remained unchanged after a short-term stimulation condition of 6 weeks and despite an increase of stimulation frequency from 130 to 200 Hz after 3 weeks. This patient underwent temporal lobectomy. Table 1 provides an overview of therapeutic interventions in each patient.

The other 10 patients entered the long-term stimulation condition and had a generator implanted. At maximal follow-up, mean stimulation output current was 2.3 V (range, 2–3 V); stimulation frequency was 130 Hz in all but one patient, who was stimulated at 200 Hz. Pulse width remained unchanged to 450 µs in all patients. Mean follow-up was 31 months (range, 12–52 months). When mean monthly seizure frequency during the last 6 months of follow-up was compared with a preintervention baseline period, one of 10 patients was seizure free (for ≥12 months); one in 10 patients had >90% reduction of seizure frequency; five of 10 patients had a reduction of seizure frequency of ≥50%; two of 10 patients had a reduction of seizure frequency of 30–49%; and one of 10 patients had a <30% seizure frequency reduction and was considered a nonresponder. Both patients who underwent resective surgery have been seizure free for ≥12 months. Table 2 provides an overview of seizure-frequency reduction per patient.

Changes in AEDs and increase in output current were allowed after 12 months of DBS. In none of the patients did this further affect seizure frequency. Table 3 shows seizure frequency at maximal follow-up and a summary of changes in AEDs and output current.

### Table 2. Follow-up duration, results of changes in seizure frequency, and side effects per patient

<table>
<thead>
<tr>
<th>Patient number</th>
<th>FU (mo)</th>
<th>Mean monthly seizure frequency before DBS or RS CPSs/GTCs/SPSs</th>
<th>Mean monthly seizure frequency after DBS or RS CPSs/GTCs/SPSs</th>
<th>Seizure-frequency reduction (%)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (DBS)</td>
<td>52</td>
<td>30/4/20</td>
<td>1 per yr/0/0.5</td>
<td>&gt;90</td>
<td>None</td>
</tr>
<tr>
<td>2 (DBS)</td>
<td>47</td>
<td>20/0/0</td>
<td>15/0/0</td>
<td>30–49</td>
<td>None</td>
</tr>
<tr>
<td>3 (DBS)</td>
<td>44</td>
<td>4/0/0</td>
<td>4/0/0</td>
<td>&lt;30</td>
<td>None</td>
</tr>
<tr>
<td>4 (DBS)</td>
<td>40</td>
<td>8/2/30</td>
<td>4/1/15</td>
<td>≥50</td>
<td>None</td>
</tr>
<tr>
<td>5 (DBS)</td>
<td>37</td>
<td>12/0/0</td>
<td>5/0/0</td>
<td>≥50</td>
<td>None</td>
</tr>
<tr>
<td>6 (DBS)</td>
<td>33</td>
<td>30/0/0</td>
<td>5 (only nightly)/0/0</td>
<td>≥50</td>
<td>None</td>
</tr>
<tr>
<td>7 (RS)</td>
<td>26</td>
<td>4/0/0</td>
<td>0/0/0</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>8 (DBS)</td>
<td>26</td>
<td>8/0/0</td>
<td>0/0/0</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>9 (DBS)</td>
<td>20</td>
<td>10/0/0</td>
<td>7/0/0</td>
<td>30–49</td>
<td>None</td>
</tr>
<tr>
<td>10 (DBS)</td>
<td>19</td>
<td>2/0/0</td>
<td>0.5/0/0</td>
<td>≥50</td>
<td>None</td>
</tr>
<tr>
<td>11 (DBS)</td>
<td>15</td>
<td>2/2/0</td>
<td>0.5/0.5/0</td>
<td>≥50</td>
<td>Asymptomatic hemorrhages along trajectory of depth electrodes</td>
</tr>
<tr>
<td>12 (RS)</td>
<td>12</td>
<td>6/0/0</td>
<td>0/0/0</td>
<td>100</td>
<td>None</td>
</tr>
</tbody>
</table>

**FU,** follow-up; **DBS,** deep-brain stimulation; **RS,** resective surgery; **CPSs,** complex partial seizures; **GTCs,** generalized tonic–clonic seizures; **SPSs,** simple partial seizures.
During the short- and long-term stimulation condition, none of the patients reported side effects. Surgical implantation of the generator and perioperative course were uneventful in all patients. None of the patients showed changes in bedside neurologic and neuropsychological testing.

DISCUSSION

The development of neurostimulation for neurological indications is driven by two major concerns related to standard available treatments. First, a general tendency is to find treatments that are minimally invasive and minimally harmful to the patient. Second, the refractoriness of some neurologic diseases and the inability to treat them with the currently available means provides an impetus to search for novel treatments.

MTL epilepsy is the most prevalent type of refractory partial epilepsy. In patients with MTL epilepsy, amygdalohippocampectomy or modified temporal lobectomy and hippocampectomy are standard procedures of choice, with postoperative long-term seizure-freedom rates of 60–75%. However, several postoperative neuropsychological studies have shown verbal memory decline after resection, mainly in left-sided operation patients, despite sufficient memory scores during the Wada test (Helmstaedter et al., 2003; Gleissner et al., 2004). Studies have shown that TLE patients without hippocampal sclerosis have a greater risk for postoperative neuropsychological deficit. The removal of nonatrophic hippocampus is associated with verbal memory decline in patients with left TLE. In right temporal lobe patients, a decline in visual-spatial learning was observed postoperatively (Trenerry et al., 1993; Stroup et al., 2003).

Patients with bilateral ictal onset are unsuitable candidates for epilepsy surgery. Patients showing widespread ictal onset have a less successful outcome after temporal lobectomy. The recurrence rate of seizures after long-term seizure freedom after temporal lobectomy is ∼15% (Keleman et al., 2006). Hence, epilepsy surgery is not an option for all patients with refractory epilepsy; it may not cure patients in the long term; it is an irreversible procedure, less successful for patients who have regional ictal onset or in patients with normal MRI; and a risk of postoperative neurologic and/or neuropsychological deficits exists. This provides an impetus for further developing alternative treatment modalities such as neurostimulation.

Strategy for a medial temporal lobe DBS pilot trial

The choice of targeting the MTL region for a pilot trial in humans at Ghent University Hospital was based on several considerations. The MTL is a region that often shows
FIG. 2. MRI image showing susceptibility artifacts of (A) left amygdalar electrode in a sagittal plane and (B) left amygdalar and hippocampal electrode and right amygdalar electrode in a coronal plane in patient 2.

Specific initial EEG epileptiform discharges as a reflection of seizure onset in human MTL epilepsy (Spencer et al., 1992). Basic research involving evoked potential excitability studies in humans and anatomic studies with tracer injections and single-unit recordings with histologic studies in animals have also confirmed the involvement of the amygdala and the hippocampus in the epileptogenic network (Wilson and Engel, 1993; Bragin et al., 2000; Kemppainen et al., 2002). Some studies have applied electrical fields to in vitro hippocampal slices with positive effects on epileptic activity (Lian et al., 2003). Bragin et al. (2002) described repeated stimulation of the hippocampal perforant path in rats showing spontaneous seizures 4–8 months after kainate injection in the hippocampus. During perforant-path stimulation, spontaneous seizures were significantly reduced. In humans, preliminary studies on stimulation of hippocampal structures showed promising results on interictal epileptiform activity and seizure frequency (Velasco et al., 2000).

Very limited data are available on the results of stimulating the ictal-onset zone itself, which is believed to consist of hyperexcitable cortex. To date, several studies have shown that DBS in MTL epilepsy has positive effects on interictal epileptiform discharges and seizures (Velasco et al., 2000; Wiebe et al., 2006). Our previously published preliminary study in three patients showed that MTL DBS in nonlesional patients leads to a significant decrease of the number of seizures and interictal epileptiform abnormalities and is a safe treatment (Vonck et al., 2002).

The present study describes a larger patient series, also including patients with structural abnormalities, who were selected for invasive video-EEG monitoring because of incongruent findings in the course of noninvasive presurgical evaluation.

**Stimulation parameters**

The stimulation parameters that were used in the present study were based on the early experience reported by Velasco et al. and by our group. The rationale for using high-frequency stimulation was that low-frequency stimulation induces EEG synchronization, whereas high frequency is associated with desynchronization, the latter condition being more likely to have a therapeutic effect in epilepsy. The rationale for increasing the stimulation frequency from 130 Hz to 200 Hz was that Osorio and colleagues suggested better seizure control in some patients when stimulation frequency was increased (Osorio et al., 2001). Carefully increasing the output current was thought to affect a larger volume of epileptic tissue, which could be useful in patients who were still having seizures after 1 year of continuous DBS. Also because of safety concerns, output currents were kept below the values used in Parkinson’s disease. Pulse width was set at 450 µs and kept unchanged throughout the study. A decrease to lower values could be feasible and based on particular stimulation paradigms used by Osorio and colleagues and lower pulse-width values applied in Parkinson’s disease. In the present trial, continuous stimulation was used. Intermittent or on-demand stimulation may become an option when DBS can be linked to seizure anticipation and detection algorithms in a closed-loop system (Le Van Quyen et al., 2001). It must be stressed that our basic assumptions with regard to stimulation parameters remain speculative, as only limited animal or human data are available on the effect of different stimulation parameters applied to temporal lobe tissue. Systematic evaluation of different stimulation parameters in experimental animal studies is urgently needed. When more information becomes available on effective stimulation parameters, the implanted pulse generator in our patients allows further adjustments in the future.

**Efficacy of DBS in MTL region**

The efficacy results of the present study further corroborate our previous findings that long-term DBS in the ictal-onset zone, as defined by invasive EEG recording,
significantly reduces seizures. Because of the open design of our study, additional antiseizure effects of simply implanting invasive electrodes cannot completely be ruled out (Boon and Vandekeerchove, 1996; Katariwala et al., 2001). Some reports in the literature support the hypothesis that actual stimulation is not necessary to achieve efficacy and claim that efficacy is based on the lesion provoked by the insertion of the electrode (Hodaie et al., 2002). This observation was described for electrode insertion in the anterior nucleus of the thalamus and referred to as “microthalamotomy.” Because in some epilepsy centers, an interval occurs between the invasive recordings and consequent resective procedures or because after the results of invasive recordings, a resective procedure was not feasible, seizure frequency after the removal of the implanted electrodes was evaluated without immediate further interventions (Katariwala et al., 2001). When the anterior nucleus is targeted, provoked lesions may be more easily effective in such a confined area compared with targets such as the MTL region. It is not impossible that in an individual patient, essential pathways could be accidentally or coincidently lesioned during MTL targeting. However, this seems an unlikely hypothesis in a series of treated patients.

In a SPECT study by Velasco et al. (2001) in six patients that underwent 3 weeks of hippocampal stimulation with subdural strips, the postimplantation SPECT (before stimulation) shows similar findings to the preimplantation images, whereas the images after 3 weeks of DBS show clear hippocampal hypoperfusion comparable to images taken after anterior temporal lobectomy. Implantation causing a lesion might be expected to provoke earlier signs of hypoperfusion in the lesioned region. Moreover, in contrast to the findings by Hodaie et al., seizures did not decrease until several days after initiation of stimulation.

It may be that the lesioning hypothesis holds true for some targets but is not applicable for others. Blinded randomization of patients to “on” and “off” stimulation paradigms after implantation for substantial periods (e.g., 6 months) might clarify this and might also simultaneously clarify the potential effect of sham stimulation of an implanted device. That patients are unaware of stimulation in MTL structures represents a favorable factor for designing blinded controlled studies in the future.

Side effects of DBS in the MTL region
Numerous reports in the literature describe the effects induced by stimulation of central nervous system structures by using implanted electrodes for diagnostic and/or therapeutic purposes in animals as well as in humans. From these studies, it has become clear that stimulation of the hippocampus predominantly affects memory functions, whereas amygdalar stimulation predominantly provokes emotional or affective–autonomic changes (Bancaud et al., 1966; Shandurina and Kalyagina, 1979). In 1969, Stevens et al. described a variety of both negative and positive emotional changes after stimulation of the amygdala and, to a lesser degree, the hippocampus in three patients who were bilaterally implanted with amygdalar and hippocampal depth electrodes for a period of ≤7 months (Stevens et al., 1969). In our study, in none of the patients were stimulation-related objective or subjective side effects found. Besides MRI, our safety data rely mainly on self-reported side effects and bedside neurologic and neuropsychological testing. Formal neuropsychological testing to assess cognitive function after long-term stimulation has been performed, and results are the topic of a separate study (Vonck et al., 2004). The lack of side effects in MTL DBS patients is most likely due to the use of different stimulation parameters. In previous studies, stimulation was often performed with the purpose of eliciting observable effects, performing functional mapping of human brain, or eliciting afterdischarges or seizure onset in the course of a presurgical evaluation. In the latter cases, stimulation frequencies usually ranged between 1 and 60 Hz, and pulse width was often 1 ms, with relatively high output currents. In our study, relatively low output currents with high frequency (130–200 Hz) and medium pulse widths of 0.45 ms were used. In none of the patients were increased seizure frequency or afterdischarges observed. This is in agreement with the preliminary findings in the short-term study from Velasco et al. (2001). Unilateral MTL DBS using similar stimulation parameters during 2–3 weeks in patients with MTL epilepsy did not produce any subjective or objective behavioral responses.

One occurrence of intracranial bleeding in the area surrounding the trajectory of the depth electrode was reported as a result of our systematic MRI screening of the correct positioning of the intracranial electrodes. Large groups of patients have been investigated with regard to the safety of conventional depth electrodes implanted for diagnostic purposes (Espinosa et al., 1994; Fernandez et al., 1997). Reported morbidity rates are no higher than 4% and most often include surgical complications such as infection and, less frequently, neurologic complications secondary to small infarcts or bleeding. Permanent sequelae occur in <1% of cases. Especially because of their size, conventional electrodes are not suitable for long-term implantation for the purpose of prolonged stimulation. From the extensive experience of DBS for movement disorders, it is known that specifically designed DBS electrodes are suitable for long-term implantation and stimulation (Rise, 2000).

Although postoperative MRI could be safely performed before the implantation of the generator, no MRIs were performed when the generator was implanted. The presence of an implanted generator limits further diagnostic workup in these patients, which has to be weighed against the potential therapeutic benefit of such a device. Future safety studies should address optimal conditions.
for generator placement and orientation and specific MRI modalities that can be safely applied in DBS patients.

**Mechanism of action of DBS for epilepsy**

Although the precise mechanism of action of DBS remains to be elucidated, local inhibition induced by applied current to a certain structure is a likely factor. This is the hypothesis of the so-called “reversible functional lesion” in which, in the case of targeting crucial structures in a network, nuclei that are involved in propagation, sustaining, or triggering of epileptic activity are inhibited. In the case of targeting an ictal focus, similar reasoning may be applied, suggesting that applied current inhibits overexcitable tissue. Apart from this “local” inhibition, the mechanism of action of DBS may be based on the effect on projections leaving from the area of stimulation to other central nervous structures. This may be the most likely hypothesis when crucial structures in epileptogenic networks are involved. However, considering that the MTL structures are also potentially involved in these networks, it may be that targeting the ictal focus may also affect the epileptogenic network. When projections from one structure to another are involved, this may be through the activation of inhibitory projections or through the inhibition of (over)excitatory projections.

**CONCLUSIONS**

This prospective, open, long-term follow-up study demonstrates efficacy of DBS in MTL structures in both lesional and nonlesional patients. Currently for lesional MTL epilepsy, resective surgery remains the preferred treatment. Beyond the issue of weighing risks and benefits for treating nonlesional MTL epilepsy, DBS clearly may have a role in nonresectable cases such as patients with bilateral MTL epilepsy. Assessment of side effects suggests that long-term DBS in the MTL region is a safe treatment. Multicenter randomized trials with a larger number of patients should now be conducted to confirm the results of the open studies. The final aim is to investigate whether DBS can be an alternative treatment for MTL epilepsy that is less invasive, reversible, and adjustable to the individual patient.

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