Original article

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Stereotactic bilateral transfrontal minimal radiofrequency thermocoagulation of the amygdalohippocampal complex for bilateral medial temporal lobe epilepsy: a retrospective study of 12 patients

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ABSTRACT – *Background.* Some patients with temporal lobe epilepsy have bilateral discharges and a few have bilateral medial temporal sclerosis. Stereotactic bilateral radiofrequency thermocoagulation (RFTC) of the amygdalohippocampal complex can terminate seizures or reduce seizure severity in patients with bilateral medial temporal lobe epilepsy (BMTLE). *Aim.* To explore the safety and efficacy of bilateral transfrontal minimal RFTC of the amygdalohippocampal complex for the treatment of BMTLE. *Methods.* A total of 12 BMTLE patients were treated with bilateral transfrontal minimal RFTC of the amygdalohippocampal complex under limited coagulations. The volumes of coagulated lesions were less than 0.6 cm^3 Clinical outcomes were evaluated using Engel's classification, the Liverpool Seizure Severity Scale (LSSS) 2.0, Wechsler Adult Intelligence Scale-Revised (WAIS-R), and Wechsler Memory Scale-Revised (WMS-R). Quality of life

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(QOL) was evaluated using the 36-item Short Form Health Survey (SF-36). *Results.* Of the 12 patients, five (42%) were assessed as Engel Class I during 12-62 months of follow-up. LSSS scores declined sharply compared with the baseline of patients not in the seizure-free category. Functions of memory and intelligence declined transiently without statistical significance ($p>0.05$) immediately after surgery, but improved significantly ($p<0.05$) six months later. The qualities of life improved except vitality. *Conclusion.* Bilateral transfrontal minimal RFTC of the amygdalohippocampal complex may terminate seizures or reduce seizure severity in patients with BMTLE. Under limited coagulations, neuropsychological function was not affected but improved along with seizure control.

Key words: bilateral medial temporal lobe epilepsy, neuropsychology, seizure severity, stereotaxy, radiofrequency thermocoagulation

Among patients with temporal lobe epilepsy, about 20-35% have bilateral discharges (Mathern *et al.*, 1989, 2002) and a few have bilateral medial temporal sclerosis (Cukiert *et al.*, 2000, 2009). After the epileptogenic zone is confirmed to be dominant on one side by stereotactic-electrode-encephalography (SEEG), resection procedures may be effective (Cukiert, 2000, 2009; de Flon *et al.*, 2010). Although most of these cases are ultimately confirmed with unilateral focus, at least 10-20% are bilateral medial temporal lobe epilepsy (BMTLE) (Spencer *et al.*, 1990; Hirsch *et al.*, 1991). For these patients, unilateral resection is less effective and bilateral damage of medial structures results in severe impairment of memory, including verbal and visual modalities (Scoville and Milner, 2000; Cheung and Chan, 2003). Deep brain stimulation (DBS) (Oh *et al.*, 2012) and vagus nerve stimulation (VNS) (Alsaadi *et al.*, 2001) may reduce seizure frequency in patients with bilateral temporal epileptic focus without neuropsychological deficits, but this does not lead to seizure freedom.

Radiofrequency thermocoagulation (RFTC) of epileptic foci in bilateral medial temporal lobes is not a new technique. As reported in the 1950s to 1970s, bilateral lesions in the amygdala, hippocampus, and fornix have been performed to control for seizures. The coagulations confined to bilateral amygdalas have been shown to be safe (Parrent and Lozano, 2000). Thus, coagulation techniques may be applicable in patients with bilateral-originated temporal seizures. Mempel *et al.* (1980) reported 70 patients with epilepsy and severe behavioural disturbances with EEG changes in the temporal regions, by performing 115 stereotactic lesions on the medial amygdala (both unilaterally and bilaterally) and anterior hippocampus (cornu Ammonis). The results regarding epilepsy were: total recovery in 11.4%, evident clinical improvement in 74.3%, and no improvement in 14.3%. Similar results were obtained for behavioural disturbances. This study indicated that bilateral amygdalotomy and unilateral hippocampotomy in selected cases may lead to recovery or amelioration and make it possible for epileptic patients with severe behavioural changes to return to normal social life (Mempel *et al.*, 1980). However, due to a lack of advanced techniques and equipment, some severe complications occur, particularly after damage of the bilateral hippocampus (Scoville and Milner, 2000). The stereotactic surgery for the treatment of temporal lobe epilepsy was gradually abandoned and was rarely reported in the last two decades of the 20th century.

With the development of magnetic resonance imaging (MRI)-guided stereotactic neurosurgery and depth-electrode-guided thermocoagulation, stereotactic epilepsy surgery underwent resurgence in Canada (Blume *et al.*, 1997; Parrent and Blume, 1999), France (Catenoix *et al.*, 2008), and the Czech Republic (Malikova *et al.*, 2009). Particularly in the Czech Republic, stereotactic amygdalohippocampectomy has been used in recent years to treat patients with temporal lobe epilepsy, with the seizure-free rate reaching 78% (Liscak *et al.*, 2010). SEEG-guided RF-thermocoagulation of epileptic foci was first reported by M. Guenot and colleagues in France with a seizure-free rate of 15% (Guenot *et al.*, 2004). Cossu reported five cases with nodular heterotopy, of whom four cases became seizure-free after stereo-EEG-guided radiofrequency thermocoagulations (Cossu *et al.*, 2014). There are a few cases of BMTLE scattered in series reports who were treated with unilateral RFTC of the amygdalohippocampal complex, but who failed to achieve seizure control (Catenoix *et al.*, 2008). Furthermore, this technique requires a radiofrequency lesion generator system connected to SEEG electrodes to produce lesions between two contiguous contacts of the selected electrodes, and the temperature cannot be monitored *in vivo* at electrode contacts. Thus, it has not been used widely. In 2013, Luo *et al.* reported one patient with BMTLE who became seizure-free after bilateral RFTC of the amygdalohippocampal complex (Luo *et al.*, 2013). However, not all BMTLE cases may be so fortunate with the treatment by RFTC.

The clinical application of bilateral stereotactic amygdalotomy was first introduced by Narabayashi in 1963. It was used for the management of patients with severe aggressive behavioural disturbances (Narabyashi *et al.*, 1963). In 2007, Kostas reported a case of self-mutilation disorder with stereotactic amygdalotomy using a bilateral transfrontal approach. Five days after the operation, the patient remained calm and sociable. Orientation, spatial judgment, visual perception, visual memory, motor speed and dexterity of the hands, and speech remained normal. The IQ measurements remained unchanged. The delayed non-matching to sample task methodology indicated no memory or learning deficits (Kostas *et al.*, 2007). These results confirmed that bilateral stereotactic amygdalotomy is safe. Therefore, we applied bilateral transfrontal minimal radiofrequency thermocoagulation of the amygdalohippocampal complex to BMTLE patients. A total of 12 patients with BMTLE after bilateral RFTC of the amygdalohippocampal complex were retrospectively analysed for the effect of both seizure control and neuropsychological functions. Patient selection, surgical technique, and effect and safety of the approach are reported as follows.

Patients and methods

Patient selection

From March 2006 to April 2011, as many as 282 cases with intrac*table* temporal epilepsy were treated by depth-electrode-guided RFTC of the amygdalohippocampal complex. Among them, 35 cases were detected using bilateral temporal epileptic discharges with four-hour scalp interictal EEG, combined with dipole source localization (DSL), as shown in *figure 1*. Non-invasive ictal EEG was not performed, in particular, because the myo-electrical noise would make the localization difficult and, moreover, the procedure for capturing attacks would require a long period of monitoring. Typical mesial temporal lobe epilepsy syndrome was excluded in all patients based on a lack of hippocampal sclerosis identified on MRI. Thus, we performed bilateral depth electrode implantation to monitor the ictal discharges in order to exclude the myo-electrical noise and confirm the epileptogenic origin. After long-term monitoring of bilateral electrode recording, 15 patients were confirmed to have unilateral temporal lobe epilepsy and five were excluded. The other 15 cases were demonstrated to have BMTLE, for which resection surgery was unsuitable. Patients were all informed about the risk of memory deficit and the possibility of poor seizure control after bilateral RFTC of the amygdalohippocampal complex, and signed the informed consent form, after which bilateral RFTC of the amygdalohippocampal complex was performed. Patients selected in this retrospective study fulfilled the following criteria and were required to:

– have taken more than two kinds of antiepileptic drugs for at least two years;

– have undergone clinical follow-up for at least one year;

– have completed pre- and postoperative evaluation for seizure outcome, including Engel's classification (Engel *et al.*, 1993) and the Liverpool Seizure Severity Scale (LSSS) (Scott-Lennox *et al.*, 2001);

– have undergone preoperative (3-7 days) and postoperative (six months) neuropsychological examinations.

One patient was lost at six months after surgery and another two refused to undergo neuropsychological examination within the follow-up time. Thus, only 12 subjects were included in this study.

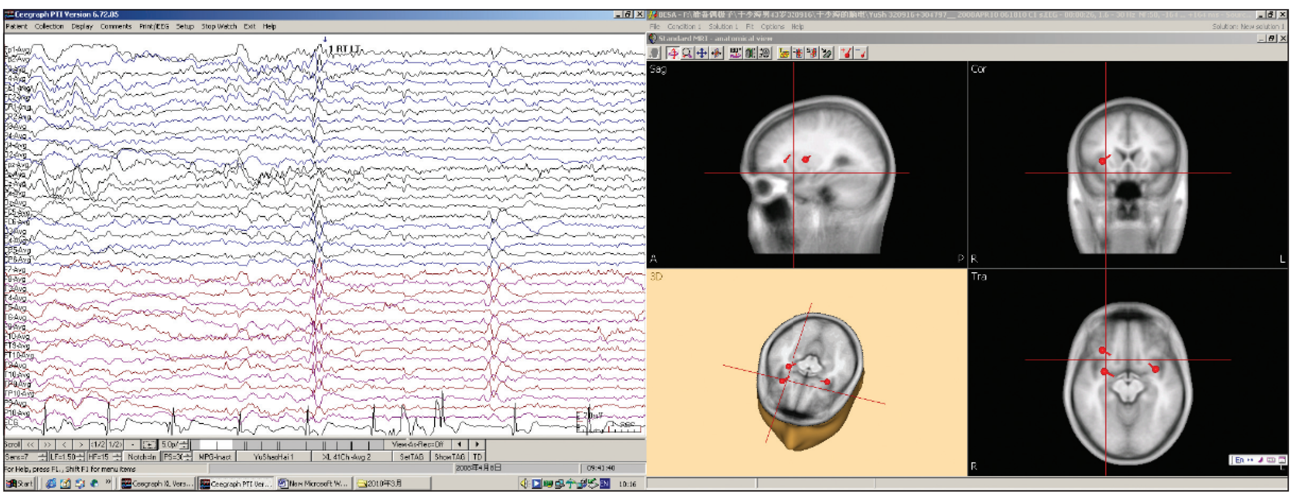

Figure 1. Bilateral temporal epileptic discharges with EEG and dipole source localization.

The 12 patients included 11 males and one female, with an average age of 29.17±8.41 (range: 14-43) years. The main causes of seizure were trauma in one, fever in one, measles in one, and unknown in nine patients. The average course of illness was 16.67±10.49 (range: 2-41) years. All patients were right-handed. The average seizure frequency during one year prior to surgery was 28.92±39.48 (range: 1-120) times per month and the average seizure severity score based on LSSS 2.0 at baseline was 58.93±10.69 (range: 22.5-77.5). Two patients revealed positive results on MRI at extra-temporal areas. Among them, one had right frontal lobe malacia and the other suffered from cerebellar atrophy. Scalp EEG with DSL indicated that all cases had bilateral temporal discharges, involving frontal lobes in nine cases, the insular lobe in one, and the parietal lobe in another. The discharges were significant on the right side in four cases, left side in five, and without side difference in three. The semiologies of all patients showed some signs of TLE, such as dysmorphopsia, eyelid blinking, oropharynx automatism, nausea, and fear or a flustered feeling, but were not clear for side localization. At the beginning of attacks, the head and eyes sometimes turned to the right or left, or the patient demonstrated hypsokinesis without deviation in most patients. As the attacks became generalized, three cases were probably dominant on the left, two on the right, and the other seven without side dominance. Preoperative neuropsychological results suggested that all index scores declined, especially for Verbal IQ (74.00±11.09), Visual MQ (78.50±13.30), and Delayed recall (74.75±12.41). Regarding behaviour, all patients complained about forgetful and bad temper of their relatives. Quality of life (QOL) was evaluated using the 36-item Short Form Health Survey (SF-36) for Physical Functioning (96.250±6.077), Role-Physical (39.583±16.714), Bodily Pain (98.000±5.326), General Health (36.667±9.847), Vitality (51.667±7.177), Social Function (42.183±9.815), Role-Emotional (44.443±16.415), and Mental Health (40.500±7.243).

Long-term-monitoring of bilateral depth electrode recording

As preoperative localization data based on MRI, scalp-video EEG, semiology, and neuropsychology led to confusion, all patients underwent invasive stereotactic bilateral depth electrode implantation. After long-term monitoring with deep-seated electrodes, two to six attacks were captured for each patient and the ictal discharges were confirmed to originate from bilateral medial temporal lobes, independently. The clinical data are summarized in *table 1*.

Targets and approaches of deep-seated-electrode implantation

The deep-seated electrodes were supplied by AD-TECH Company and had eight contacts. The interval of contacts was 5 mm (SD08R-SP05X-000) and 10 mm (SD08R-SP10X-000), respectively. The implantation of electrodes was performed using the Leksell stereotactic system. For economic reasons, we were restricted by the number of electrodes used, limiting different targets. The only two target points were placed at bilateral amygdalas (5 mm anteromedial to the temporal horn of the lateral ventricle). As the frontal lobe was involved in discharges according to scalp EEG in most cases, four electrodes were implanted with bilateral temporal (SD08R-SP05X-000) combined with frontal (SD08R-SP10X-000) approaches in such a way that they were vertical to the hippocampal axis, as shown in *figure 2A*. For one patient with parietal involvement, six electrodes were implanted; two (SD08R-SP10X-000) with a parietal-occipital approach along the hippocampal axis (*figure 2B*).

Diagnosis of BMTLE

Although bilateral temporal lobe discharges are not rare clinically, only cases with independent ictal discharges from bilateral medial temporal lobes can be diagnosed as BMTLE. The electrodes from trans-bilateral temporal lobes to amygdalas were essential for the diagnoses (*figure 2A*). The first two contacts were located in the medial temporal lobe. Only the spikes derived from the first two contacts during the beginning of attacks were a confirmation of MTLE. In this study, all patients were found to have independent discharges from bilateral medial temporal lobes during the interictal period. For each patient, at least two attacks were observed during monitoring and the ictal discharges were confirmed to be of bilateral medial temporal lobe origin.

Figure 3 shows the epileptic discharges of one patient from trans-lateral temporal electrodes. The first two contacts were located in the medial temporal lobe (*figure 3A*). Interictal discharges were found in the medial aspect of bilateral temporal lobes (*figure 3B*). During the first attack, the rhythmic discharge activity started from the left medial temporal lobe and then spread to the right (*figure 3C*). The second attack originated from the right medial temporal lobe without spreading to the left (*figure 3D*). This is a typical case of BMTLE.

The clinical characteristics, including MRI, EEG+DSL, and origin of ictal discharge during long-term monitoring of depth electrode recordings are shown in *table 1*.

Table 1. Clinical characteristics and corresponding examinations.

Patient	Sex	Age (year)	Cause	Course (year)	Semiology	MRI	EEG+DSL	Origin of ictal discharge
1	M	28	Unknown	12	Dysmorphopsia Head turn (L)	Neg	Bit+ Ins.R	R for 4; L for 2
2	M	29	Unknown	24	Flustered Limbsclonus (L)	Neg	Bit+ L	R for 1; L for 2
3	M	43	Unknown	41	Nausea Head turn (L or R) Limb rigor and clonus (R)	Neg	Bit, R	R for 1; L for 1
4	M	21	Unknown	16	Eyelid blinking Upper limb clonus	Neg	Bit+	R for 2; L for 1
5	M	32	Trauma	18	Fear Limb clonus (L)	R frontal malacia	Bit, L	L for 1; R for 2
6	F	44	Unknown	7	Flustered Head turn (L or R) Upper limb clonus	Neg	Bit+, R	R for 2; L for 1
7	M	14	Unknown	5	Nausea Impaired version (L or R)	Neg	Bit+, Par. R	R for 3; L for 2
8	M	25	Unknown	10	Oropharynx automatism Psychiatric symptoms	Neg	Bit+, L	R for 3; L for 4
9	M	25	Unknown	18	Oropharynx automatism Angulus oris tic	Neg	Bit, L	R for 5; L for 1
10	M	30	Fever	25	Eyelid blinking Upward stare Head hypsokinesis without deviation	Neg	Bit+, L	R for 1; L for 2
11	M	33	Measles	16	Dysmorphopsia Turning of head and eyes (R)	Cerebellar atrophy	Bit+, R	R for 2; L for 1
12	M	26	Unknown	18	Eyelid blinking Upward stare Head hypsokinesis without deviation	Neg	Bit+	R for 2; L for 2

Bit: bilateral temporal; Bit+: bilateral temporal plus frontal; DSL: dipole source localization; Ins: insula; L: to the left; Neg: negative; Par: parietal; R: to the right.

The technique of RFTC

The target points were placed in bilateral amygdalas with a transfrontal approach perpendicular to the long axis of the hippocampus through the same skull perforation of depth electrode recording. With efforts to avoid the ependymal surface of the lateral ventricle and potential cortical vessels, the trajectory was presupposed by first passing through the insular lobe to the hippocampal head, passing the amygdala and parahippocampus, and then further reaching the skull base.

Steps of the procedure

– (1) A scalp cut (length: 3 mm) and a percutaneous drill into the skull (diameter: 2 mm) were made in the frontal area.
– (2) The dura was punctured using a sharp needle.
– (3) A blunt needle was slowly rotated into the cortex to reach the skull base through the target point.
– (4) A depth electrode was implanted successively after withdrawing the blunt needle.
– (5) Epileptogenic regions, confirmed by long-term monitoring of depth electrode recording, were

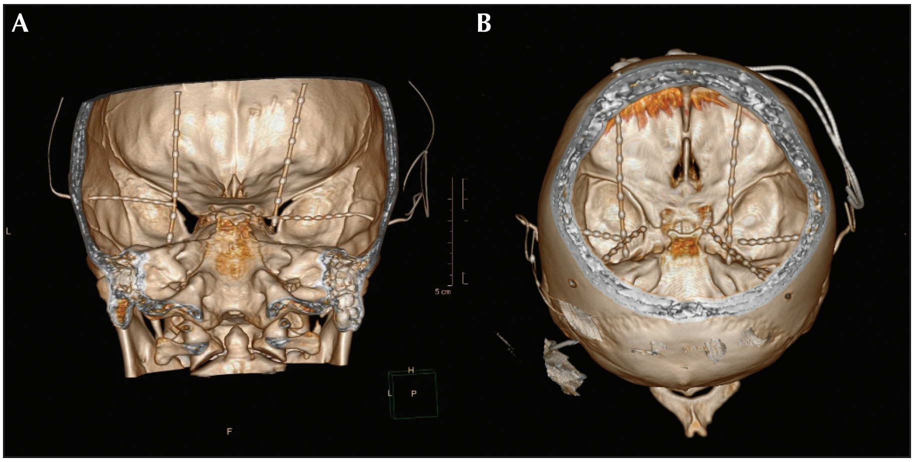

Figure 2. Implantation of deep-seated electrodes. Implantation with four (A) and six (B) electrodes.

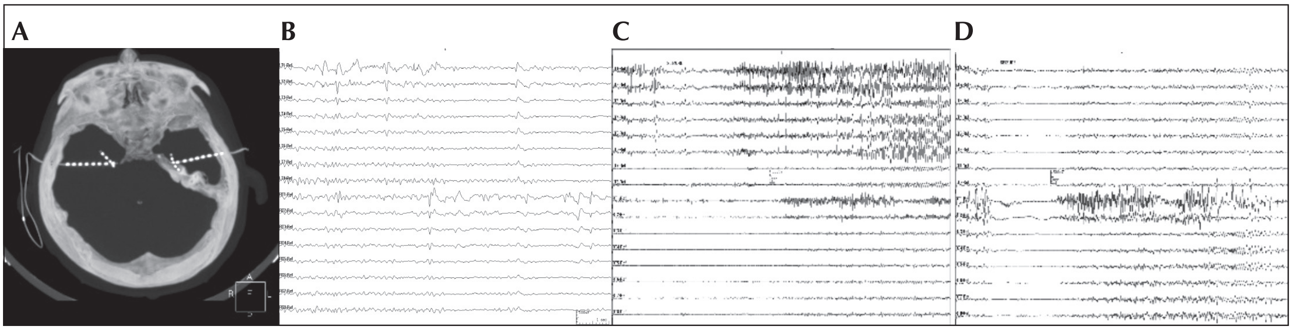

Figure 3. (A) A CT scan shows the position of electrodes. (B-D) Epileptic discharges from trans-lateral temporal lobe electrodes. The first eight lines (LT1-LT8) show the EEG recording from the left electrode. The first line is the recording of the top contact located in the left medial temporal lobe. The lines 9-16 (RT1-RT8) represent the right electrode and line 9 corresponds to the top contact in the right medial temporal lobe. (B) Interictal monitoring shows bilateral independent discharges (LT1, LT2, RT1, RT2). (C) Activity from the left medial temporal lobe spread to the right (from LT1 and LT2 to RT1). (D) Activity from the right medial temporal lobe without spreading (RT1 and RT2).

retailored by the intraoperative recordings of interictal discharge. For precise localization, the top contact of depth electrodes was first reached to the skull base and then withdrawn at intervals of 3 mm at a time during the recordings.

– (6) A lesioning probe was used to stimulate the epileptogenic zone for functional evaluation, initially to preserve the optic tract and trigeminus.

– (7) The "tailored epileptogenic region" was then coagulated (75°C, 120s, with 3-mm interval) only in the area without clinical response, such as blinking of the eyes or twitching of the face during stimulations under 2 volts.

– (8) Subsequently, discharges from lesions were redetected using depth electrodes. If the epileptic discharges were still remarkable, further coagulation was repeated in order to make them disappear or to significantly decrease them.

Evaluation of clinical outcomes of seizure control

Using Engel's classification (Engel *et al.,* 1993) and LSSS 2.0 (Scott-Lennox *et al.,* 2001), seizure outcomes were evaluated every six months post surgery by an experienced member of staff who was aware of the date of operation but did not know what kind of surgery was performed. The LSSS 2.0 questionnaire produces a single unit-weighted scale that measures the severity of the most severe seizures the patient experiences during the recall period. This revised scoring system repositions the severity score to range from 0 (no seizures) to 100 (most severe possible).

Neuropsychological evaluation

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Wechsler Memory Scale-Revised (WMS-R) were

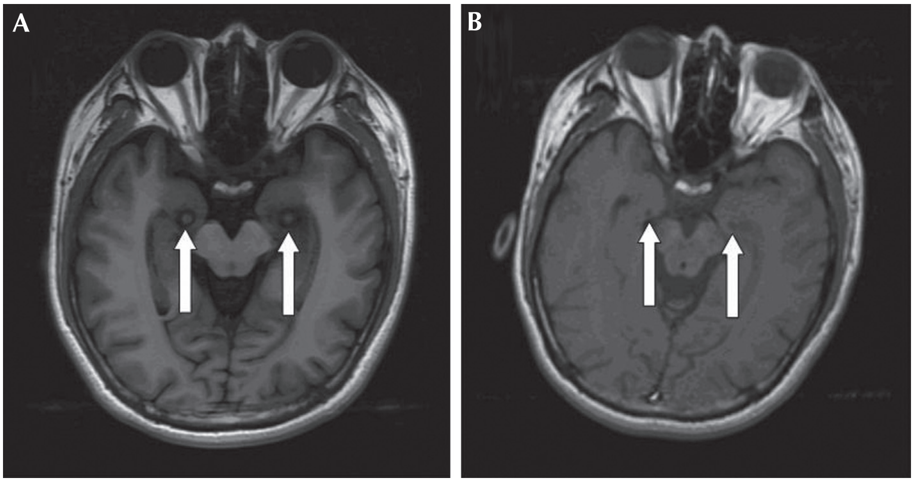

Figure 4. Postoperative MRI. (A) Axial slices showing acute MRI changes in the bilateral medial temporal lobe. (B) MRI scan revealing the coagulation lesions of bilateral amygdalohippocampal complexes one year after surgery.

used to assess a total of 12 subjects, 3-7 days preoperatively and six months after the surgery, by a neuropsychologist. The indices in WAIS-R include General intelligence quotient (IQ), verbal IQ, and performance IQ. WMS-R includes Global Memory quotient (MQ), Verbal Memory quotient, Visual Memory quotient, Attention/Concentration, and Delayed Recall as indices. Furthermore, QOL was evaluated using the 36-item Short Form Health Survey (SF-36) for Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Function, Role-Emotional, and Mental Health.

Statistical analysis

Statistical analyses were performed using the IBM SPSS 20.0. Data are expressed as mean±SD. Studied variables, including scores of WAIS-R, WMS-R, and LSSS 2.0, were confirmed by Gaussian distribution using the One-Sample Kolmogorov-Smirnov test. To assess the impact of coagulation on neuropsychological function, tests of Between-Subjects Effects were applied to compare the scores obtained at different times. The paired sample *t*-test was used to measure the variation in seizure severity, as well as QOL before and after surgery.

Results

Surgery-related parameters

The target point placed in the amygdala was expressed as zero. With transfrontal trajectory, lesions above the target point were expressed as positive numbers and those under the target point as negative numbers. The coagulation was based on the extent of discharge from SEEG combined with intraoperative depth electrode recordings. Coagulation (75°C; 120 s; interval: 3 mm) was performed at sites of discharges, at least 3 mm above the base of the skull. MRI examination revealed fresh lesions encompassing the complexes of the amygdala, hippocampus, and a few parahippocampal gyri, bilaterally. Mild peripheral ring oedema and haemorrhagic foci were observed during this period (*figure 4*)*A*. The volume of lesions was approximately calculated as 0.4757±0.0842 cm^3 on the left and 0.4545±0.0864 cm^3 on the right side, according to MRI performed immediately after the surgery ($V= l\pi r^2$, with l being the length of lesions and r the radius of each lesion). All lesions corresponded to less than 0.6 cm^3. There was no statistically significant difference in the volume of the lesions between the left and right side (t=0.672; p=0.515). Post-coagulation discharges were evaluated as reduced (>50%), significantly reduced (>75%), and disappeared. There were no side effects or specific complaints during the postoperative period. All patients were advised to take antiepileptic drugs preoperatively and continue with them for at least two years after the surgery with no change in dose. Postoperative MRI, one year after the surgery, revealed very small structural damage in the areas of the bilateral amygdalohippocampal complex (*figure 4B*).

Clinical outcomes with respect to seizures

The follow-up time was 12-62 months. Every patient included completed at least one year of follow-up; eight with two years, five with three years, three with four years, and two with five years. Five cases were classified as Engel Class I (seizure-free), two as Engel Class II (rare seizures), three as Engel III (significantly reduced seizure frequency), and two as Engel Class IV

Table 2. Parameters during surgery and outcomes of seizure control during follow-up.

Patient	Side	Extent[1] (mm)	Extent[2] (mm)	Extent[3] (mm)	Discharges[4]	Lesions	Volume (cm^3)	Follow-up (months)	Engel classification
1	L R	-15~-5; -13	-19~-9; -13~0	-16~-7; -10~-1	Reduced Sig. reduced	4 4	0.4239 0.4239	62	2c
2	L R	-11~-1; -13~-3	-11~-1; -10~0	-9~0; -10~-1	Sig. reduced Reduced	4 4	0.4239 0.4239	60	2b
3	L R	-21~-11; -13	-21~-1; -13~-8	-18~-1; -13~-7	Disappeared Sig. reduced	7 3	0.6500 0.3391	56	1c
4	L R	-7~7; -18~2	-7~3; -18~-5	-5~3; -15~-5	Reduced Reduced	4 5	0.3956 0.4522	42	4c
5	L R	-15~5; -17~3	-10~0; -17~-2	-10-~-1, -15; -14~-2, -14~0	Sig. reduced Reduced	5 11	0.5652 0.5652	41	3a
6	L R	-14~-4; -19~-1	-9~1; -4~1	-9~1, -3~1; -7~3	Reduced Reduced	7 5	0.4522 0.4522	28	3a
7	L R	-9; -18~-8	-14~-5; -18~-5	-9~0; -15~-3, -3	Disappeared Sig. reduced	4 6	0.4239 0.5087	24	1a
8	L R	-18~-3; -19~-4	-18~-2; -19~-6	-15~0; -16~-1	Disappeared Disappeared	6 6	0.5935 0.5935	21	1a
9	L R	-15~5; -18~2	-15~-5; -18~-3	-12~-4, -2; -15~-3, -1	Reduced Reduced	5 6	0.4522 0.5652	20	4b
10	L R	-14~-4; -8	-14~1; -8~2	-11~1; -5~3	Disappeared Disappeared	5 4	0.5087 0.3956	12	1d
11	L R	-12~-2; -17~-7	-12~-2; -17~-8	-9~-1; -14~-8	Sig. reduced Sig. reduced	4 3	0.3956 0.3391	19	1d
12	L R	-16~-6; -18~2	-13~0; -15~0	-9~0; -10~-2	Reduced Reduced	4 4	0.4239 0.3956	24	3b

The target placed in the amygdala with transfrontal trajectory was expressed as 0; the points above target were expressed as positive (+) numbers and those under the target as negative (-). The unit of extent was mm and volume was cm3. With an interval of 3 mm for the extent of discharges, coagulation was made at least 3 mm above the base of the skull.
[1]extent of ictal discharges on preoperative SEEG;
[2]extent of interictal discharges on intraoperative recording;
[3]extent of coagulation;
[4]the reduction of discharges after coagulation based on intraoperative recording;
Sig: significant.

(negligible change). Age, volume of lesion, number of RFTC, epilepsy duration, *etc.* were not related to the outcomes of seizure control. Only the decrease in intraoperative recording discharge after coagulation was a predictor of outcome.

Surgery-related parameters are summarized in *table 2*. Seven patients, not categorized as seizure-free, were re-evaluated by LSSS 2.0 after surgery (mean±SD: 39.29±10.87) and their average severity scores significantly declined (mean±SD: 19.64±6.84) compared with

Table 3. LSSS 2.0 scores of seven patients not categorized as seizure-free.

	Patient 1	Patient 2	Patient 4	Patient 5	Patient 6	Patient 9	Patient 12	Mean±SD
Before surgery	45	65	57.5	62.5	77..5	55	50	55.83±7.53
After surgery	17.5	37.5	42.5	45	52.5	42.5	37.5	39.29±10.87
Improvement	27.5	27.5	15	17.5	25	12.5	12.5	19.64±6.84

Paired sample *t*-test: t=7.603, $p<0.001$

Table 4. WAIS-R and WMS-R scores before and after surgery.

	Before surgery	3-7 days after surgery	6 months after surgery	P^1	P^2	P^3
Full scale IQ	76.25±10.03	73.17±7.59	80.17±5.47	0.030*	0.007	0.000**
Verbal IQ	74.00±11.09	72.50±8.86	80.83±9.03	0.390	0.001	0.000**
Performance IQ	77.67±12.51	76.17±8.96	81.25±10.50	0.203	0.005	0.000**
Global MQ	76.58±11.66	76.17±9.49	80.67±10.31	0.684	0.001	0.000**
Verbal MQ	78.50±13.30	77.42±12.76	81.67±11.41	0.189	0.001	0.000**
Visual MQ	71.50±11.52	71.92±8.61	74.58±9.10	0.691	0.007	0.017*
Attention	76.58±18.23	75.25±14.70	81.83±14.83	0.496	0.012	0.002*
Delayed recall	74.75±12.41	73.50±11.83	76.42±9.57	0.314	0.184	0.025*

Tests of Between-Subjects Effects: *significant; **highly significant
[1]difference between before and 3-7 days after surgery;
[2]difference between before and 6 months after surgery;
[3]difference between 3-7 days and 6 months after surgery.

baseline (t=7.603; $p<0.001$). The outcomes are summarized in *table 3*.

Neuropsychological results

Compared with scores before and immediately after surgery, Full Scale IQ significantly decreased (p=0.030) and the other indices declined a little, but without significance ($p>0.05$). Compared with scores before and six months after surgery, there was a statistically significant increase ($p<0.05$) in all indices, except Delayed Recall (p=0.184). Compared with scores immediately and six months after surgery, there was a statistically significant increase ($p<0.05$) in all indices. Neuropsychological results, including intelligence (WAIS-R) and memory (WMS-R), at different times are summarized in *table 4*.

Furthermore, after RFTC, all patients became calm and sociable without any behavioural disturbances. Their relatives were even more satisfied than the patients themselves because of their reduced bad temper. The postoperative qualities of life with SF-36 evaluation for Physical Functioning (96.667±4.924), Role-Physical (64.583±16.714), Bodily Pain (98.000±5.326), General Health (68.083±10.157), Vitality (49.750±7.557), Social Function (69.448±10.725), Role-Emotional (63.891±17.166), and Mental Health (57.667±10.299) were analysed using a paired sample *t*-test, as shown in *table 5*.

Discussion

For BMTLE patients, bilateral resection of medial structures results in severe impairment of memory (Scoville and Milner, 2000; Cheung and Chan, 2003). Deep brain stimulation (Oh *et al.*, 2012) and vagus nerve stimulation (Alsaadi *et al.*, 2001) may reduce seizure frequency without neuropsychological deficits, but few patients become seizure-free. The clinical application of bilateral stereotactic amygdalotomy was first used for the management of patients with severe aggressive behavioural disturbances (Narabyashi *et al.*, 1963). The results confirmed that bilateral transfrontal stereotactic amygdalotomy is safe (Kostas *et al.*, 2007). Therefore, we applied bilateral minimal radiofrequency thermocoagulation of the amygdalohippocampal complex to

Table 5. Improvement of quality of life.

	Pre-operation	Post-operation	t	P
Physical Functioning (PF)	96.250±6.077	96.667±4.924	-0.561	0.586
Role-Physical (RP)	39.583±16.714	4.583±16.714	-4.062	0.002*
Bodily Pain (BP)	98.000±5.326	98.000±5.326	0.000	1.000
General Health (GH)	36.667±9.847	68.083±10.157	-6.114	0.000**
Vitality (VT)	51.667±7.177	49.750±7.557	1.305	0.219
Social Function (SF)	42.183±9.815	69.448±10.725	-7.641	0.000**
Role-Emotional (RE)	44.443±16.415	63.891±17.166	-2.548	0.027*
Mental Health (MH)	40.500±7.243	57.667±10.299	-4.106	0.002*

Paired sample *t*-test: *significant; **highly significant

BMTLE patients. The diagnosis of BMTLE, surgical technique and effect of RFTC, and neuropsychological studies are discussed as follows.

Requirement of long-term depth electrode recording for BMTLE diagnosis

In bilateral temporal lobe epilepsy (BTLE), ictal epileptic discharges originate from both sides independently (Mathern *et al.*, 1989). According to earlier reports, MRI reveals bilateral medial temporal lobe sclerosis in only a few BTLE patients (Cukiert *et al.*, 2000, 2009). In this study, four to six electrodes were placed in the medial temporal lobe bilaterally using a different approach. Since the first three contacts of each electrode were focused in the medial part of bilateral temporal lobes, the epileptogenic discharge from the medial temporal lobe would certainly be captured. For economic reasons, we were unable to place as many electrodes as we would have liked for the SEEG recording, thus the epileptogenic zone in the extra-temporal lobe could not be localized with this kind of monitoring, however, it was at least possible to distinguish insular lobe epilepsy and lateral temporal lobe epilepsy from BMTLE using trans frontal and lateral electrodes, separately.

In our group, scalp EEG, combined with dipole source localization, indicated that epileptic discharges were concentrated at bilateral medial temporal lobes in 35 cases among the total 282 patients. The recording of depth electrodes indicated that ictal discharges originated from bilateral medial temporal lobes independently in 15 patients. Among the 12 patients included in this retrospective study, the semiology matched some signs of temporal lobe epilepsy, but only two patients were positive on MRI; one had right frontal lobe malacia which was dissonant with other diagnostic information and another had cerebellar atrophy which was meaningless with regards to localization. Although scalp EEG combined with dipole source localization indicated that epileptic discharges were concentrated at bilateral medial temporal lobes, some unilateral or extra-temporal lobe epilepsy was excluded by long-term recording of depth electrodes. For economic reasons, we were unable to place a large number of electrodes for SEEG monitoring. Our purpose was to diagnose BMTLE. In the absence of any correlation of waves originating from the first two or three contacts of the implanted electrodes during the beginning of attacks, the patient was excluded. Four to six electrodes were sufficient for the diagnosis of BMTLE. The 2 or 3-dimensional implantation of electrodes to the medial temporal lobe could precisely locate the epileptogenic zone of BMTLE. Although we were unable to locate the epileptogenic zone in other areas, the use of lateral electrodes excluded a lateral temporal lobe origin, frontal electrodes excluded a frontal or insula origin, and parietal-occipital electrodes excluded a parietal-occipital origin.

A transfrontal approach led to the coagulation of amygdala, hippocampus and parahippocampal gyrus together as one trajectory

A transoccipital approach is more popular, as reported recently (Blume *et al.*, 1997; Parrent and Blume, 1999; Parrent and Lozano, 2000; Malikova *et al.*, 2011). However, as coagulation should be produced bilaterally, the volume of lesions must be controlled in order to spare the main structures of the hippocampus, to preserve memory and related functions (Scoville and Milner, 2000; Cheung and Chan, 2003). It was therefore unnecessary to extend lesions to the hippocampus body through a transoccipital trajectory. In our cases, the

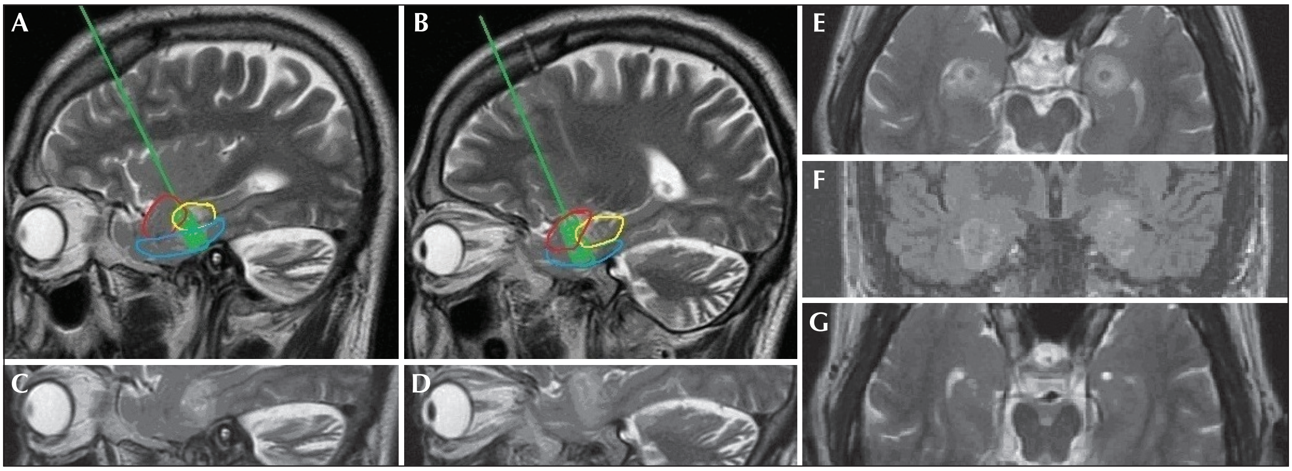

Figure 5. Transfrontal trajectory and coagulation zone. Red circle: amygdala; yellow circle: hippocampal head; blue circle: parahippocampus; green line: trajectory; green area: coagulation zone. (A) Coagulations on the right; (B) coagulations on the left; (C) true coagulations on the right; and (D) true coagulations on the left. (E) Axial section of early MRI; (F) coronal section of early MRI; and (G) MRI one year after surgery.

ictal discharges mostly arose from the anterior part of the hippocampus and its junction with the amygdala, as well as the parahippocampus gyrus under the target area during the monitoring. Furthermore, since the transfrontal trajectory passes through the insular lobe, this is very helpful for identifying insular lobe epilepsy during depth electrode monitoring, both pre and intra-operation. Thus, we placed electrodes using a transfrontal trajectory from the frontal cortex to the insular lobe, and then from the target point to the base of the skull in order to coagulate the complexes of the amygdala, hippocampal head, and part of the parahippocampal gyrus together, as well as to distinguish insular lobe epilepsy, which was not possible using an occipital approach.

Intraoperative recording combined with preoperative monitoring ensured precise coagulation, limiting the lesion

In order to ensure that the coagulation was precise, some experts (Guenot *et al.,* 2004; Catenoix *et al.,* 2008; Cossu *et al.,* 2014) use a radiofrequency lesion generator system to connect to SEEG electrodes, to produce lesions between two contiguous contacts of the selected electrodes. This technique ensures coagulation in the precise area of epileptic discharges, but the temperature cannot be monitored *in vivo* at electrode contacts and special equipment is required. Since no such equipment exists in our hospital, the procedure described here clearly consists of neither SEEG, nor SEEG-guided RF-thermocoagulation. We refer to our technique only as "depth electrode-guided RFTC". During the operation, the depth electrode was replaced to record interictal discharges and then the lesioning probe was replaced to coagulate the epileptogenic zone. In order to make the procedure more precise and specific to each patient, intraoperative recordings were combined with the results of ictal monitoring to guide the coagulation. Therefore, coagulation was produced in the precise epileptogenic zone of amygdalohippocampal complexes with limited lesions.

In *figure 5*, the green line is the transfrontal trajectory and the green area represents the coagulation zone. The amygdala is marked with a red circle, the head of hippocampus in yellow, and the parahippocampus in blue. The coagulation zone was determined according to the information of ictal origin from preoperative monitoring combined with interictal discharges from the intraoperative recording. The coagulations were mostly located in the hippocampal head and parahippocampus on the right side (*figure 5A*, *figure 5C*). On the left side, the coagulation zone involved the hippocampal head and parahippocampus, as well as the amygdala (*figure 5B*, *figure 5D*). Early MRI revealed that the hippocampal head and parahippocampus were coagulated on both sides, but that the amygdala was only coagulated on the left side (*figure 5E*, *figure 5F*). One year after surgery, the coagulation lesion in the amygdala was clearly visible on the left but not on the right side (*figure 5G*), and hippocampal bodies were not involved on either side. Therefore, the coagulations were made individually according to the pre- and intra-operative recordings, and not only according to anatomical structures. Minimal coagulation was possible in which hippocampal bodies remained, thus memory functions were preserved after RFTC of the bilateral amygdalohippocampal complex.

A more precise evaluation of outcome based on Engel's classification combined with LSSS

Engel's classification (Engel *et al.,* 1993) is widely used to evaluate the clinical outcome of seizure control postoperatively. However, seizure severity is another important outcome in the clinical evaluation of antiepileptic therapy. Antiepileptic therapy can modify seizure severity as perceived by the patient, without altering seizure frequency. As Engel's classification relates to seizure frequency more than severity, LSSS 2.0 (Scott-Lennox *et al.,* 2001) was used in this series before and after surgery. The severity score was decreased by 19.64±6.84 after surgery (p<0.001) in seven patients not categorized as seizure-free. For these patients, complete remission of seizures was not possible, but a decrease in seizure severity could increase their QOL.

A decrease in intraoperative recording discharge after coagulation as a predictor of seizure control outcome

In patients assessed as Engel Class I, post-coagulation discharges all disappeared or were significantly reduced. However, in patients assessed as Engel Class III or IV, the decrease in post-coagulation discharges was less. On the other hand, patients who had significant decrease in post-coagulation discharges (at least on one side) also had a significant reduction in seizure severity score (*e.g.* Patients 1 and 2; *table* 2). No relationship between seizure control and number of lesions or volume of coagulation was observed (Malikova *et al.,* 2011). Some patients experienced more coagulations, but a failure to control seizures was observed (*e.g.* Patients 4, 5, 6, 9 and 12; *table 2*), which indicates that a large area of ictal discharge might only be the seizure onset or irritated zone, and not the epileptogenic zone (Rosenow *et al.,* 2001). Conversely, patients whose discharges were significantly reduced, with ideal outcome, after a low level of coagulation indicate that the lesions derived from within the epileptogenic zone opportunely (*e.g.* Patient 11; *table 2*). Therefore, the large area of ictal discharge during depth electrode recording might be the prognostic factor for poor outcome of seizure control before performing RFTC.

Safe treatment of BMTLE using bilateral RFTC of the amygdalohippocampal complex with limited volume based on neuropsychological studies

In this study, we were deeply worried about the damage to memory and intelligence after bilateral RFTC of the amygdalohippocampal complex. Thus, the coagulation was made in a relatively limited volume. Indeed, as expected, scores of most neuropsychological indices were decreased immediately after surgery, especially for General IQ which statistically declined with significance (p=0.030). The transient decline of scores of neuropsychological indices may have been caused by acute damage to the bilateral medial structures of the temporal lobe. However, the deficiency of memory and intelligence could be ignored as the volume of coagulation was safe enough (less than 0.6 cm^3 on each side). In fact, all scores of WAIS-R and WMS-R indices increased significantly six months later, except Delayed Recall (p=0.184). This improvement might be correlated with the gradual recovery of medial structures of the temporal lobes and the decreased seizure frequency or severity (Kwan and Brodie, 2001; Suthana *et al.,* 2012). Although the IQ and MQ of the patients improved six months after operation, none of the patients' IQ or MQ scores reached normal level, even for seizure-free patients. In particular, for Delayed Recall scores remained the same pre-operatively. Indeed, the baseline was relatively low for BMTLE patients, but we still doubted that the bilateral coagulation limited the recovery of IQ and MQ. Further study should be performed in seizure-free patients receiving DBS and VNS.

With regards to behaviour, after operation, all patients became calm which was more appreciated by their relatives. However, this kind of calmness could be explained as less activity which could have impaired their QOL. Although no patients complained about the decline of QOL, further evaluation of QOL was required to substantiate the data. Therefore, we performed an evaluation of QOL for patients with SF-36. The Physical Functioning and Bodily Pain remained at a high value after operation. The General Health and Social Function improved very significantly. The Role-Physical, Role-Emotional, and Mental Health improved significantly. However, Vitality was a little worse but without significant difference. This might reflect the results of bilateral coagulations of amygdalas. Thus, we emphasize that the bilateral coagulations must be limited to within a volume of 0.6 cm^3, otherwise the Vitality declines significantly. This is the most risky part of the procedure. Furthermore, although the Role-Physical, General Health, Social Function, Role-Emotional, and Mental Health improved, the respective scores remained at a relatively low level. This may be because the baseline of QOL for BMTLE patients before operation was at almost the lowest level. We expect that DBS or VNS would improve the QOL for BMTLE patients, to a high degree.

Conclusion

A total of 12 subjects were included in this retrospective study, who were ultimately diagnosed with BTLE by means of long-term depth electrode recording and treated by bilateral minimal RFTC of the amygdalohippocampal complex using a transfrontal approach. Individual coagulation was guided by intraoperative depth electrodes combined with preoperative recordings. Seizure frequency and severity were evaluated using Engel's classification, as well as LPSS 2.0, and the results were relatively optimistic. A relationship between post-coagulation discharges and outcome of seizure control was identified. The safety of bilateral RFTC of the amygdalohippocampal complex was confirmed by a neuropsychological study. After the operation, the qualities of life were improved, except for Vitality. Therefore, bilateral RFTC of the amygdalohippocampal complex could be considered as a promising method in addition to DBS and VNS for patients with BTLE. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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The authors have no conflicts of interest to declare.

Ethics and consent.
The study was approved by the ethics committees, both of the Navy General Hospital of PLA and The 306th Hospital of PLA. All human studies were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Patients' parental guardians gave their informed consent prior to their inclusion in this study. Due to the retrospective nature of the included participants of this investigation, subsequent informed written consent of the enrolled participants was not necessary according to the ethics committees.

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TEST YOURSELF

EDUCATION

(1) Describe the recommended anatomical approach for bilateral RFTC of the amygdalohippocampal complex for the treatment of BMTLE described here.

(2) What is the limitation of the volume for coagulation on each side?

(3) What is the neuropsychological effect of bilateral RFTC of the amygdalohippocampal complex?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".