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Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients

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ABSTRACT

Introduction: The cognitive and behavioral effect of deep brain stimulation (DBS) administered to the deep cerebral nuclei for epilepsy treatment is unknown. We investigated the cognitive outcomes at least 12 months after DBS to the bilateral anterior thalamic nucleus (ATN) for controlling intractable epilepsy.
Methods: Nine patients with intractable epilepsy who were not candidates for resective surgery, but who were treated by bilateral ATN DBS underwent cognitive and behavioral assessments before implantation and more than 1 year after DBS surgery. Postoperative cognitive assessments were carried out under a continuous stimulation mode.
Results: The mean seizure-reduction rate of these patients after ATN DBS was 57.9% (35.6–90.4%). Cognitive testing showed favorable results for verbal fluency tasks (letter and category, $p < 0.05$), and a significant improvement in delayed verbal memory was observed ($p = 0.017$). However, we did not observe any significant changes in general abilities (IQ, MMSE), information processing (digit forward and backward, Trail A, and Digit Symbol), or executive function (Trail B and WCST). Interestingly, we did not observe any significant cognitive decline approximately 1 year (mean, 15.9 months) after ATN DBS surgery.
Conclusions: We showed that ATN DBS not only resulted in promising clinical effects but was also associated with improvements in both verbal recall and oral information processing, which may be related to the bilateral activation of the fronto-limbic circuit following DBS surgery. Further controlled, long-term studies with larger populations are warranted for elucidating the clinical effects of ATN DBS.

1. Introduction

In spite of introduction of modern anti-epileptic drug (AED) therapy, state-of-the-art of epilepsy surgery, and vagus nerve stimulation (VNS), approximately 30% of patients continue to have refractory seizures.[1,2] Deep brain stimulation (DBS) via an implanted neuro-stimulator system has been recognized as a promising, alternative therapeutic choice for epilepsy.

Among various neural targets for DBS, the anterior nucleus of thalamus (ATN) has been considered a good locus for seizure control.[3,4] Very recently, the results of a randomized, double blind, multicenter trial (SANTE, Stimulation of the Anterior Nucleus of Thalamus for Epilepsy) were released showing favorable therapeutic efficacy on refractory partial or secondary generalized epilepsy.[5]

Various adverse neuropsychological changes may occur after DBS surgery used to control movement disorders such as Parkinson's disease, essential tremor, or dystonia.[6] Therefore, a careful and meticulous neuropsychological (NP) testing has been a routine and indispensable procedure ahead of the surgical implantation to pre-empt serious post-surgical adverse effects. However, to the best of our knowledge, no previous report has examined the cognitive changes in detail after ATN DBS in patients with refractory epilepsy.

The aim of this study was to investigate the long-term cognitive effects of bilateral ATN stimulation in patients with refractory epilepsy using a comprehensive NP testing.

2. Methods

2.1. Patients

Patients were enrolled for bilateral ATN DBS based on the following criteria: frequent (more than 4 per a month) and disabling seizures not controlled by multiple antiepileptic drugs (AEDs) treatment; not candidates for resective surgical treatment

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Table 1
Demography of our patients with ATN DBS implantation.

Patient	Diagnosis	Sex	Age	F/U (M)
1	B F-TLE, cryptogenic	F	28	60
2	Multifocal epilepsy, double cortex (B P-O)	F	14	52
3	Multifocal epilepsy (P-O dominant), cryptogenic	F	23	48
4	B FLE, symptomatic previous meningioma resection (frontal)	M	50	28
5	B C-PLE, cryptogenic	M	36	27
6	B TLE, symptomatic (B HS)	M	34	25
7	B C-PLE, cryptogenic	M	43	25
8	B P-OLE, symptomatic (B perisylvian PMG)	M	31	24
9	Multifocal epilepsy, B schizencephaly	F	42	22

HS: hippocampal sclerosis; FLE: frontal lobe epilepsy; F-TLE: fronto-temporal lobe epilepsy; C-PLE: centro-parietal lobe epilepsy; P-OLE: parieto-occipital lobe epilepsy; PMG: polymicrogyria.

as determined by video-EEG monitoring (e.g. multifocal ictal onset zone); patients (or caregivers) agreed to keep a daily seizure diary for a 3-month baseline period before DBS implantation and continuously after initiation of treatment; patients (or caregivers) agreed that no changes to the baseline presurgical medication regimen would be made during at least the first year after DBS implantation. The study was approved by the institutional review board of Catholic University of Korea, and informed written consent was obtained from all patients or their family members.

From our initial series of fifteen patients who completed at least 1 year follow-up after implantation, 9 patients were included in this study (Table 1). Six patients were excluded from these reasons: three with a considerable cognitive derangement from mental retardation (IQ < 70), not adequate for our comprehensive NP testing; the other 3 patients underwent only one session of NP assessment, two refused a participation in the follow-up examination, the other was not tested during the pre-operative period.

2.2. Procedures

The presurgical evaluations performed were video EEG monitoring, optimum 1.5-T MRI, SPECT, 18-FDG PET, and full neuropsychological assessment.

Our NP testing was composed of the Mini-Mental State Examination (MMSE), the Korean Wechsler Adult Intelligence Scale (K-WAIS), Rey–Kim Memory Test (RKMT),[7] the Korean Memory Assessment Scale (K-MAS),[8,9] the Grooved Pegboard Test,[10] the Wisconsin Card Sorting Test (WSCT),[11] and the frontal-lobe function test; Trail Making Test (TMT-A and B), the Digit-Span Test, the Word Fluency Test (category and letter), the Digit-Symbol Substitution Test, and the Frontal Assessment Battery (FAB).[12]

The Rey–Kim Auditory Memory Test[7] is a standardized Korean version of the Rey Auditory Verbal Learning Test, which is known to be a reliable measure in the detection and identification of faulty memory mechanisms. The administration includes five successive presentations of a list of 15 words followed by free recall, a 20-min delayed recall, and a 20-min delayed recognition trial. Delayed recognition was measured with a list of 50 words in which the subject was instructed to circle words from the learning list. The FAB test[12] included tests of similarities, lexical fluency, motor series, conflicting instructions, go-no-go, and prehension behavior. Higher the scores on these tests represented better NP performance, except for the Trail Making Test and the Grooved Pegboard Test, for which lower scores indicated better results.

The insertion of DBS electrodes (model 3387; Medtronic®, Minneapolis, MN) and implantable pulse generators (IPG, model Soletra; Medtronic®) was previously described.[3,4] Electrode positioning was verified by postoperative CT (seven patients) or MRI (two patients). Activation and programming of IPG started 1 week (seven patients) after implantation.

Our stimulation protocols of ATN DBS are differentiated from the previous reports[2,3]: intermittent adjustment in stimulation parameters (frequency 100–185 Hz, voltage 1.5–3.1 V, pulse duration 90–150 μs, continuous stimulating mode, and in one or two stimulated DBS electrode contacts (monopolar configurations)) were carried out in all patients.[1]

All patients underwent the same NP testing with the implantable pulse generator (IPG) in the ON state at least 12 months after ATN DBS surgery. Stimulation parameter settings remained unchanged for at least 2 weeks before evaluation. Between the two time points, all patients were under the same or slightly adjusted antiepileptic drug (AED) dosage, and minimal change (less than 1 AED) was made in their pre-operative AED composition (Table 2).

Table 2
Antiepileptic drugs (AEDs) during baseline and at the time of follow-up neuro-cognitive assessment.

Patient	AEDs (/day)	Baseline levels in μg/mL (therapeutic range)	AEDs used at the time of the follow-up NPT (/day)	Mean post-implantation AED levels (SD) in μg/mL	Duration of seizure free state just before the follow-up NPT (day)
1	CBZ 900 mg, LTG 400 mg[a]	CBZ 9.8 (8.0–12.0)	CBZ 600 mg, LTG 400 mg[a]	CBZ 9.1 (3.2)	14
2	VPA 250 mg, LTG 400 mg[a], TPM 200 mg[a]	VPA 37.1 (50–100)	VPA 250 mg, LTG 300 mg[a], LEV 1500 mg[a], TPM 100 mg[a]	VPA 39.3 (8.8)	<1[b]
3	CBZ 800 mg, TPM 300 mg[a], LTG 200 mg[a]	CBZ 9.6 (8.0–12.0)	CBZ 400 mg, TPM 300 mg[a], LTG 200 mg[a], PGB 300 mg[a]	CBZ 8.2 (2.4)	5
4	VPA 1000 mg, TPM 100 mg[a], OXC 1200 mg[a]	N/A	VPA 1000 mg, TPM 100 mg[a], OXC 1200 mg[a]	VPA 77.5 (6.6)	9
5	VPA 1000 mg, LTG 400 mg[a]	VPA 68.4 (50–100)	VPA 1000 mg, LTG 300 mg[a], LEV 1000 mg[a]	VPA 70.0 (9.3)	2
6	VPA 1200 mg, TPM 200 mg[a], LTG 100 mg[a], PGB 150 mg[a]	N/A	VPA 1200 mg, TPM 200 mg, LTG 100 mg, PGB 300 mg	VPA 91.8 (10.2)	6
7	VPA 1000 mg, LTG 100 mg[a]	VPA 49.8 (50–100)	VPA 1000 mg, LTG 100 mg	VPA 53.1 (4.6)	21
8	CLB 15 mg[a], CBZ 800 mg, VPA 500 mg, LTG 200 mg[a]	CBZ 8.9 (8.0–12.0); VPA 36.3 (50–100)	CLB 10 mg[a], CBZ 800 mg, VPA 500 mg, LTG 200 mg[a]	CBZ 8.6 (2.4); VPA 45.9 (7.8)	5
9	LEV 1000 mg[a], LTG 200 mg[a], CLB 10 mg[a]		LEV 1000 mg, LTG 200 mg, CLB 10 mg		4

N/A: not available; CBZ: carbamazepine; VPA: valproate; TPX: topiramate; DPH: phenytoin; VGB: vigabatrin; LMT: lamotrigine; CLB: clobazam.
[a] AED serum levels not measurable at the time or not followed.
[b] The patient's seizures were very frequent and much clustered (More than 95% of her seizures have been generated during breakfast). But there were no complex partial seizures or generalized seizures observed during the NPT by examiner.

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Table 3
Seizure frequencies of the patients during long-term follow-up.

Patient	Baseline	1 year	2 years	3 years	4 years	5 years	Mean seizure reduction[a]
1	6.3 (1.2)	3.8 (0.8)*	3.3 (1.5)*	2.3 (1.0)†	3.1 (1.3)†	3.1 (0.4)†	50.8%
2	630.5 (71.9)	576.6 (104.5)	521.8 (121.1)	468.3 (98.4)	406.0 (89.6)		35.6%
3	5.9 (0.8)	4.5 (1.2)	4.7 (0.9)	3.6 (0.5)*	2.8 (0.8)†		52.5%
4	12.0 (1.1)	4.2 (1.9)†	5.5 (2.2)*				54.2%
5	14.2 (2.3)	11.0 (2.4)	8.4 (4.7)				40.8%
6	10.4 (1.3)	2.0 (0.6)†	1.0 (0.8)†				90.4%
7	4.3 (0.7)	1.7 (0.6)†	1.1 (0.5)†				74.4%
8	15.8 (3.7)	8.0 (3.4)*	6.3 (3.9)*				60.1%
9	16.1 (4.8)	7.1 (3.1)*	6.0 (2.8)†				62.7%

Values given as absolute numbers of seizures per month (SD). Baseline seizure frequency: the number of seizures per month during 3 months before implantation.
[a] The ratio of the number of seizures during the last 3 months/that of baseline.
* $p \leq 0.05$ (Wilcoxon rank sum test comparing yearly seizure rate with baseline).
† $p \leq 0.01$ (Wilcoxon rank sum test comparing yearly seizure rate with baseline).

2.3. Statistical analysis

Continuous variables with a normal distribution were analyzed using paired *t*-tests to investigate differences between baseline and post-operation NP results. When continuous variables showed an asymmetric distribution, the Wilcoxon rank sum test was performed.

We also used linear regression models to further evaluate the relationship of long-term clinical outcome and neuro-cognitive changes to each of the twenty-seven domains of our NP testing. Statistical significance of all tests was evaluated at a significance level of 0.05. Statistical analyses were performed using SPSS 12.0 (SPSS, Inc., Chicago, IL).

Table 4
Mean change in scores on neuropsychological variables between baseline and post DBS.

Neuropsychological variable	Baseline (mean ± SD)	Post DBS – baseline[a] (mean)	*p* value†
IQ			
Verbal IQ	85.7 ± 11.0	1.8	0.40
Performance IQ	90.8 ± 12.4	0.3	0.85
Total IQ	88.6 ± 9.7	1.4	0.42
Rey–Kim Memory Test (RKMT)			
Delayed verbal recall	6.8 ± 3.1	2.2	**0.017**
Verbal recognition	9.3 ± 2.2	0.3	0.47
Rey figure drawing	8.0 ± 5.1	−0.5	0.6
Rey figure immediate recall	6.1 ± 4.3	0.2	0.62
Rey figure delayed recall	5.8 ± 4.1	−0.2	0.59
MQ (memory quotient)	81.2 ± 11.8	3.8	0.06
Korean version of Memory Assessment Scales (K-MAS)			
Short term memory	78.5 ± 21.0	0.0	1.00
Verbal memory	79.2 ± 16.9	6.2	0.17
Visual memory	81.6 ± 18.7	1.8	0.72
Total memory	77.3 ± 17.1	5.3	0.16
Frontal lobe function and attention			
MMSE	25.3 ± 3.7	−0.1	0.85
Trail Making Test			
Time on part A	90.8 ± 80.6	5.4	0.81
Time on part B	140.0 ± 119.7	−4.5	0.89
Digit Span forward	6.1 ± 2.1	−0.3	0.34
Digit Span backward	3.6 ± 1.9	0.1	0.78
Word Fluency Test			
Category	18.2 ± 7.2	2.5	**0.03**
Letter	17.4 ± 10.1	5.2	**0.043**
Digit Symbol	7.2 ± 3.0	−0.2	0.68
Frontal Assessment Battery	14.7 ± 3.2	0.2	0.72
Pegboard test			
Right hand	240.7 ± 219.2	0.1	0.99
Left hand	248.8 ± 225.7	−25.7	0.36
Wisconsin Card Sorting Test			
Number of correct responses	37.3 ± 15.5	7.0	0.10
Perseverative errors	40.5 ± 16.5	4.7	0.36
Nonperseverative errors	45.3 ± 11.2	−0.7	0.88

[a] Changes from baseline to the end of the long-term phase (NP testing score at least 12 months after baseline evaluation).
† *p* values in boldface are statistically significant ($p < 0.05$, paired *t*-test).

3. Results

3.1. Demographic characteristics of patients

The age of patients at surgery ranged from 14 to 49 years. Four patients were male. The duration of epilepsy ranged from 8 to 39 years. All patients had experienced more than 2 years of post-operative follow-up, ranging from 22 to 60 months (mean 34.6 ± 16.6 months). Post-operative NP assessments were performed after more than 1 year (mean 15.9 ± 5.0 months) after the ATN DBS operation.

All nine patients had complex partial seizures evolving to secondary generalized seizures. Their ictal onsets were not lateralized or were multifocal (Table 1). After long term follow-up, 7 (77.8%) of our patients experienced a significant reduction in their seizure frequency (>50% seizure reduction). The overall mean seizure-reduction rate of nine patients after ATN DBS was 57.9% (35.6–90.4%, Table 3).

3.2. Neuropsychological data

Results were favorable for the word fluency tasks (letter and category, $p < 0.05$), and a significant improvement was observed on the RKMT of delayed verbal memory ($p = 0.017$) after DBS procedures. There were no significant changes in general abilities (IQ, MMSE), information processing (digit forward and backward, Trail A, and Digit-Symbol Substitution), or executive function (Trail B, FAB, and WCST). Detailed neuropsychological testing results are described in Tables 4 and 5.

Intriguingly, there was no statistically significant correlation between clinical effect after ATN DBS (seizure reduction rate) and the NP measurements; delayed verbal recall ($r = 0.505$, $p = 0.17$), Word Fluency Test (letter, $r = -0.276$, $p = 0.47$; category, $r = -0.011$, $p = 0.98$), as well as the other NP domains (verbal, performance and total IQ; short term, visual and total memory; various frontal lobe function tests including TMT-A and B, and WCST).

4. Discussion

ATN is a collection of deep nuclei thought to affect not only the modulation of alertness but also learning and memory. Prior clinical studies have shown that ATN dysfunction may be

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Table 5
Raw data of NP testing at baseline before surgery and after chronic ATN DBS.

	Patient									*p*-Value*
	1	2	3	4	5	6	7	8	9	
Verbal IQ										
Baseline	106	82	78	71	112	79	95	72	101	0.40
Post-op	100	78	81	73	123	78	98	74	98	
Performance IQ										
Baseline	112	71	70	75	106	89	96	74	86	0.85
Post-op	112	75	73	71	103	90	96	83	89	
Full scale IQ										
Baseline	109	75	71	73	110	82	95	72	94	0.42
Post-op	105	76	82	71	116	88	97	75	93	
Delayed verbal recall										
Baseline	8	9	9	6	7	1	11	4	8	**0.017**
Post-op	9	8	10	9	10	6	11	8	11	
Word Fluency Test										
Category										
Baseline	31	19	24	15	21	13	19	16	20	**0.03**
Post-op	37	18	24	17	28	15	15	15	24	
Letter										
Baseline	24	13	24	14	24	12	34	5	18	**0.043**
Post-op	43	19	20	13	27	16	42	14	19	

* Comparison of data measured at baseline vs. post-ATN DBS operation state; *p*-values in boldface are statistically significant ($p < 0.05$, paired *t*-test).

associated with deficits in declarative memory (semantic and episodic memory).[13]

However, cognitive decline after chronic ATN DBS has not been noticed in some case studies.[3,4] Only a brief and limited description on the general intelligence quotient (IQ) test results after ATN DBS was reported.[14] In SANTE trial, a subjective deterioration of memory function was reported in 13% of patients during the initial period (for 3 months after surgery). But it was neither serious in severity nor maintained chronically (all resolved over 12–476 days).[5] To our knowledge, we now provide the first long-term NP data concerning the full cognitive function of ATN DBS patients with intractable epilepsy.

Our patients did not show any meaningful decline in various NP domains after chronic ATN stimulation. Moreover, word fluency and delayed verbal memory were significantly improved after the procedure. We can hypothesize several underlying mechanisms of the beneficial effects observed after ATN DBS on cognition besides its antiepileptic effects.

First, we assumed that electrical stimulation of ATN also directly activated the limbic memory circuit and the associated thalamo-cortical pathway, resulting in significant improvement in verbal memory or verbal fluency after chronic stimulation. This hypothesis is supported by some recent studies. Bilateral ATN stimulation of the rat brain reversibly increased glucose uptake in connected thalamic nuclei and both hippocampi, which might be attributed to excitation of efferent thalamo-hippocampal projections from the ATN.[15] A case study with long-term hypothalamic/fornix stimulation for controlling morbid obesity provided interesting data showing that hippocampus-dependent memory improvement originated from the activation of the hippocampal memory circuit through stimulation of the fornix.[16] In that case, the hypothalamic/fornix stimulation also induced some improvement of verbal fluency (phonemic and semantic). This may reflect a contributing role of the medial temporal regions not only to memory but also to language, due to their close interaction with neighboring neocortical structures specialized in language processing,[17] such as perirhinal cortex[18] in our ATN DBS patients.

Second, we can suppose that the improved cognitive function originated from decreased AED dosage or reduced seizure frequency. Four among our patients had been under topiramate (TPM), which is most likely to induce deficits in working memory, and verbal fluency.[19,20] Minimal reduced dosage of TPM in one patient (400–300 mg per day, patient 2) was accompanied by supplementing the levetiracetam (LEV) for controlling her refractory seizures. LEV administration may have a favorable impact or even improvement in some of NP measures, such as attention, verbal fluency and memory functions.[21–23] But the minimal AED compositional change and dosage adjustment did not seem to have a great influence on the overall neuro-cognitive data we observed in this study (Tables 2 and 5), especially on patient 2 (whose delayed verbal recall and categorial word fluency did not improve after ATN DBS).

Third, we could find that a good clinical outcome was not a univariate predictor of any of the NP domains. There was no difference in the NPT data obtained between our seven patients (patients 1, 3, 4, 6, 7, 8 and 9), who achieved more than a 50% seizure reduction, and the other patients (patients 2 and 5) with $\leq$50% reduction (data not shown). Finally, we cannot exclude a practice effect from repeated NP assessment may not be excluded. However, practice is likely to have had a minimal or negligible effect on follow-up NP testing performed at least 1 year post-surgery.

In conclusion, the effects of bilateral ATN DBS on cognition shown here represent an interesting collateral effect in the context of antiepileptic treatment for intractable epilepsy. Clinical considerations regarding ATN DBS for treating refractory epilepsy are in the early stages, and additional convincing data of the chronic influence of DBS on the cognition or behavior will be forthcoming.

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