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Clinical commentary

Neuropsychological consequences of pallidal deep brain stimulation altering brain networks

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ABSTRACT

The purpose of this study was to evaluate postoperative changes in the neuropsychological function of cervical dystonia patients who had undergone deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi) and to investigate how DBS affects neuropsychological function by altering the neural networks of the brain. In 12 cervical dystonia patients, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used to measure the preoperative and postoperative status of cervical dystonia, and the Seoul Neuropsychological Screening Battery was used to gather neuropsychological data. The data were analyzed using a Wilcoxon signed-rank test. The average improvement in the TWSTRS score at the time of the postoperative neuropsychological battery was 56.1 ± 26.8%. In the neuropsychological battery, inhibitory control, as evaluated by the Stroop test, was significantly decreased after GPi DBS. The average pre-/postoperative Stroop test word and color reading correct response score were 107.9/99.2 ($P = 0.043$) and 85.3/75.8 ($P = 0.032$), respectively. The observed neuropsychological consequence of GPi DBS in this study, i.e., decreased inhibitory control, implies that electrical stimulation of the GPi may alter brain networks via the centromedian-parafascicular nuclear complex, suppressing the inhibitory control function of the prefrontal cortex.

1. Introduction

Cervical dystonia, one of the most common types of idiopathic focal dystonia, is characterized by sustained and involuntary neck muscle contraction that results in abnormal posture and pain [1]. The pathogenesis of dystonia is known to include 1) maladaptive neuroplasticity that induces abnormal cortical representation and/or disorganized striatal synaptogenesis; 2) abnormal low-frequency neural oscillations between the subthalamic nucleus (STN) and globus pallidus internus (GPi) that are correlated with dystonic muscle contraction; and 3) abnormal cerebellothalamo-cortical networks [2–5]. Deep brain stimulation (DBS) at the posterolateral ventral GPi is as an effective treatment modality for many types of idiopathic dystonia including cervical dystonia [6,7]. GPi DBS desynchronizes abnormal low-frequency oscillations and induces delayed long-term benefits via reorganization of maladaptive neuroplasticity [3,8].

DBS exerts its therapeutic effects not only by suppressing neural activity at the targeted region but also by activating brain networks relevant to the target via orthodromic and antidromic axonal connections [8–10]. In this way, GPi DBS modulates neural signaling in the pallidothalamic, striatopallidal, and subthalamopallidal networks [11–13]. The GPi, the principal output structure of the basal ganglia, participates in the sensorimotor, associative, and limbic systems using its inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [13]. Many previous reports have addressed the neuropsychological outcomes of DBS in Parkinson's disease patients [14]. To the best of our knowledge, however, few studies have addressed the neuropsychological consequences of GPi DBS in cervical dystonia patients [15]. Hypothesizing that GPi DBS might somehow influence neuropsychological outcomes, we collected neuropsychological battery data from cervical dystonia patients who had undergone DBS since February 2012. In this study, we analyzed the differences between pre- and postoperative data from these patients, and the results were interpreted as they related to brain network alterations.

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2. Materials and methods

The design of this study was authorized by the local institutional review board for clinical studies. Consecutive patients with idiopathic cervical dystonia who underwent GPi DBS between February 2012 and August 2015 were considered for this study. A diagnosis of cervical dystonia was made if all of the following criteria were met: significant history of involuntary contraction of the neck muscles, typical dystonic activity on electromyography, absence of organic cerebral disease other than small vessel disease, and no evidence of psychological disease history, as assessed by a specialist from the Psychology Department. Neuropsychological examinations were conducted for all of the patients planning to undergo DBS. Baseline and follow-up neuropsychological examinations were conducted in 12 patients, and these 12 patients were included in this study. Symptoms of cervical dystonia were evaluated using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) pre- and postoperatively.

2.1. Neuropsychological examination

The Seoul Neuropsychological Screening Battery, which is one of the most commonly used tests for evaluating Korean populations, was used to evaluate neuropsychological functions [16]. The Seoul Neuropsychological Screening Battery consists of several individual tests: the digit span forward and backward tests, which assess attention; the Korean Boston Naming Test (K-BNT) with calculations, which assesses language and related function; the Rey Complex Figure Test (RCFT) copy score, which assesses visuospatial function; the immediate recall, delayed recall and recognition tests of the Seoul Verbal Learning Test (SVLT), which assess verbal memory; the immediate recall, delayed recall and recognition tests of RCFT, which assess visual memory; the Controlled Oral Word Association Test (COWAT), which assesses generative naming; and the Korean Color-Word Stroop Test (K-CWST), which assesses inhibitory control. The Korean Mini Mental State Examination (K-MMSE), the Global Deterioration Scale (GDS), the Neuropsychiatric Inventory (NPI, administered to patients and caregivers), the geriatric depression scale, the Instrumental Activities of Daily Living (IADL) scale, and the Clinical Dementia Rating (CDR) scale were also applied during the same clinical visit.

2.2. Operative procedures

We have previously reported our surgical procedures elsewhere, and this procedure is briefly described here [3,17,18]. Stereotactic magnetic resonance images (MRI, MAGNETOM Avanto 1.5 T, Siemens Co., Washington, D.C., USA) were obtained while a Leksell frame (Elekta, Kungstensgatan 18, SE-103 93 Stockholm, Sweden) was fixed on the patient's skull. The target was identified as the most ventral point in the posterior third of the GPi, just above the optic tract. The electrode implantation procedures were performed under local anesthesia, and microelectrode recordings were conducted using three channels after careful burr-hole trephination. Stimulation-relevant benefits and adverse effects were examined after macrostimulation, and the final location for the permanently implanted electrodes (model 3387, Medtronic, Minneapolis, MN, USA) was determined. After the DBS electrode was implanted, the final lead locations were confirmed via fluoroscopy.

2.3. Statistical analysis

In this study, the number of enrolled patients (12) limited the statistical analysis to non-parametric methods. The Wilcoxon signed-rank test was performed to compare pre- and postoperative data from the TWSTRS and the neuropsychological battery. To differentiate the secondary effects of motor-functional improvements, correlation analyses between improvement rates of TWSTRS scores and improvement rates of neuropsychological scores were also performed. All analyses were performed with two-tailed tests, and the significance level was defined as $P < 0.05$.

3. Results

The patient characteristics are summarized in Table 1. The median (range) age, disease duration, and education duration were 56 (35–71), 3.3 (1.3–12.8), and 9 (0–16) years, respectively. All of the patients were right-handed and were within the normal range for neuropsychological status except emotional perception from the dystonic symptoms. The TWSTRS scores were significantly improved after GPi DBS at the 3-months follow-up ($P = 0.002$), and delayed benefits were also observed (Fig. 1). The average TWSTRS improvement rate at the time of the follow-up neuropsychological examination was 56.1 ± 26.8%. There were no statistically significant changes in K-MMSE, GDS, NPI, geriatric depression scale, IADL or CDR scores. The average amplitude, pulse width and frequency were 3.98 ± 0.56 V, 81.3 ± 22.9 μs and 143 ± 18.8 Hz, respectively. Low-frequency stimulation (60–80 Hz) was not used in our patients because patients could not withstand the lower frequency during subsequent parameter adjustment ses-

Table 1
Patient characteristics.

No.	Sex	Age	Disease duration (m)	Follow-up duration (m)	Follow-up exam*	Baseline/follow-up		Stimulation parameters (right/left hemisphere)†
						K-MMSE	TWSTRS	
1	F	54	49	48	11	29/27	42/0	3.3, 90, 130/3.8, 90, 130
2	M	55	53	45	11	30/30	56/31	4.4, 90, 130/4.5, 90, 130
3	M	71	24	37	7	29/28	52/32	3.5, 90, 150/3.5, 60, 130
4	F	41	15	33	4	28/30	76/16	4, 60, 150/4, 60, 150
5	F	61	39	33	4	30/30	37/29	3.5, 120, 180/3.5, 150, 180
6	M	56	154	26	3	28/30	47/32	4, 60, 150/4, 90, 150
7	F	60	35	25	5	30/30	47/23	3.6, 90, 130/3.6, 90, 130
8	M	65	35	25	5	26/29	52/40	3.7, 90, 130/3.8, 60, 130
9	F	35	37	22	4	27/26	58/11	4, 60, 130/4, 60, 130
10	F	40	40	21	5	30/29	40/23	3.5, 90, 130/3.8, 90, 130
11	F	72	96	14	5	16/15	46/24	5.5, 52, 180/5.5, 52, 180
12	F	67	40	11	4	28/24	48/11	4.2, 90, 130/4.2, 78, 150

Abbreviations: Korean Mini-Mental Status Examination (K-MMSE), Toronto Western Spasmodic Torticollis Scale (TWSTRS).
* This column indicates when the post-operative neuropsychological battery was performed, in number of months after deep brain stimulation.
† Stimulation parameters indicate the amplitude (V), pulse width (μsec), and frequency (Hz) for each hemisphere, respectively.