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Anatomical situation of the subthalamic nucleus (STN) from mid-commissural point (MCP) in Parkinson's disease patients underwent deep brain stimulation (DBS): an MRI targeting study

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Abstract

Introduction: It is demonstrated that the degree of clinical improvement in Parkinson's disease (PD) achieved by deep brain stimulation (DBS) is largely dependent on the accuracy of lead placement. In addition, individual variability in the situation of subthalamic nucleus (STN) is responsible for spatial inter-individual fluctuations of the real patient's target.

Objective: Our study was aimed to identify the anatomic location of STN from midcommissural point (MCP) in Iranian Parkinson's disease patients who underwent DBS by means of a 3-dimentional magnetic resonance imaging (MRI).

Methods:Forty-six patients with the PD were recruied as candidates for bilateral implantation of STN-DBS (92 subthalamic nucleuses) were recruited. All these patients had bilateral implantation at the same operation. DBS and MRI parameters including the target coordinates (X, Y, Z) and the distances from MCP to the center of STN in all three axes on both sides were reported and calculated for each patient.

Results: The location of STN was approximated by a site with 11 mm lateral, 3 mm inferior and 3 mm posterior to the midcommissural point. This distance was significantly lower in PD patients who aged >50 years in both right and left sides in the Y-axis direction.

Conclusion: Our findings led to a considerable set of information which could help neurosurgeons during DBS procedure in Iranian PD patients. Despite the differences observed between various population of PD patients in the anatomical location of STN, our results further depicted the clustration of active contact points in same region.

Keywords: Parkinson's disease, deep brain stimulation (DBS), subthalamic nucleus (STN), midcommissural point (MCP), Anatomical situation, magnetic resonance imaging (MRI).

Introduction

Parkinson's disease (PD), a neurological disorder with the cardinal features of bradykinesia, shuffling gait, postural instability, tremor, and loss of automatic movement, affects between 100 and 200 per 100,000 people over 40 years old, and over 1 million people in North America alone [1-3]. The emergence of pathologic activity in the subthalamic nucleus (STN), globus pallidus pars externa (GPe), and globus pallidus pars interna/substantia nigra pars reticulate (GPi/SNr) are the most common

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characteristics of PD [4,5].

Although, pharmacologic treatment is the most effective symptomatic therapy and the initial treatment for PD, however, it is accompanied with some complications [6], and therefore, several surgical procedures have been studied in advanced PD including deep brain stimulation (DBS). After the pioneering study of Benabid et al [7] and Pollak et al [8] in 1993-1994, the preferred surgical treatment for medically refractory PD is chronic high frequency stimulation of the STN [9-11]. Previous evidences show that despite the relatively small size, ovoid shape, and oblique disposition of the STN, it can be targeted for the treatment of movement disorders with considerable results [12,13]. Nowadays, it is demonstrated that the degree of clinical improvement achieved by DBS is largely dependent on the accuracy of lead placement [14,15]. In past, different methods have been used to determine the location of the STN. One of the methods employs a line drawn from the anterior commissure (AC) to the posterior commissure (PC) and calculates the mid commissure point [16]. This can be defined using three dimensional magnetic resonance imaging (3D-MRI).

On the other hand, individual variability in the situation of STN is responsible for spatial inter-individual fluctuations of the real patient's target, which might significantly differ from the theoretical statistical target. Therefore, a direct visualization of the STN on special MRI sequences is a suitable method for accurate localization [15,17]. Nonetheless, regarding the goal of this method was achieved the best result and accurately localizing of the target prior to and during surgery, the MRI of the whole brain is vital to identify the STN and important landmarks such as the anterior and posterior commissures and red nucleus [18].

To understand the importance of this variability, we aimed to identify the anatomic location of STN from midcommissural point (MCP) in Iranian Parkinson's disease patients who underwent DBS by means of a 3-D MRI. The knowledge to the variation in anatomic situation of STN can be vital in determining the best area for deep brain stimulation in patients with Parkinson's disease Fig. 4.

Method

Patients: This prospective study was conducted at Parkinson clinic of Rasoul-e-Akram University Hospital in Tehran, Iran during 2006-2008, and 46 patients with diagnosis of PD were selected for bilateral implantation of STN-DBS (92 subthalamic nucleuses). The study was approved by the institutional board and informed consent was obtained from all patients.

The clinical diagnosis was made by at least one movement disorders specialists based on a detailed history and neurological examination using accepted criteria. The United Kingdom Brain Bank, clinical criteria as modified by Douglas et al [19] were used to diagnose PD cases. The patients' symptoms have been assessed in off drug clinical situation.

Patients with medically refractory motor fluctuation were offered surgery. More detaied inclusion criteria for DBS were primary (idiopathic) uncontrolled PD, age below 75 years, good residual response to Levo-dopa intake-test (amelioration >40%) and Unified Parkinson's Disease Rating Scale (UPDRS III) (drug-off) over 40. Additional, surgical contraindications included impaired general status , history for psychiatric disorders, cardiac failure, taking anticoagulants, pacemakers in sentinel mode and dementia.

Baseline and demographic informations including current age, duration of PD and dominant site of symptom were all recorded for each patient before DBS.

Surgical and MRI procedures: 46 patients met the criteria for DBS. They all had bilateral implantation for the same operation. The L-dopa was withholden 24 hours before surgery,

while dopamino-agonists were tapered 72 hours before.

For stereotactic frame fixation, the Leksell-G head frame was fixed to the patient's skull under local or general anesthesia. It was tried to fix the frame parallel to the orbitomeatal axis. Then patients were transferred to the MRI suite, where special sequences obtained by a 1.5 Tesla machine (Philips). The series of images were taken pre-operatively included: 3-dimentional MR T1-weighted, MR T2-weighted coronal, axial images and inversion recovery (IR).

The localization of the STN target was performed on coronal and axial T2-weighted images acquired perpendicularly to AC-PC axis, crossing the anterior limit of the Red Nucleus. Then the target coordinates (X,Y,Z) were reported to the T1-weighted image in order to find the best trajectories for insertion of DBS electrode. Firstly, the center of STN was determined and then the anatomical STN coordinates were calculated in comparison with midpoint of the AC-PC line (MCP) to find the distance of this nucleus from MCP. The distance was calculated using three methods: manual, stereotactic software (steronata) and Schaltenbrand -Wahren stereotactic atlas.

In the operating room, the head frame was fixed on the operating table to perform a bicoronal incision and a 14mm diameter burr holes were done to the patient's skull according to pre-operative trajectories. Five microelectrode recorder were inserted into the brain and subsequently electrophysiologic monitoring simultaneous was done. After finding the best point of stimulation, the permanent leads were inserted and fixed to the skull. Finally, under general anesthesia, wires were tunneled and the pulse generator (Kinetra) placed subcutaneously in the chest wall. The pulse generator was connected to the permanent leads.

DBS and MRI parameters such as target coordinates (X,Y, Z) and the distances from MCP to the center of STN in all three axes on both sides were reported and calculated for PD patients.

Variable	Value
Current age (year) mean±SD	49.93±8.95
Gender distribution (%)	
Male	37 (80.4%)
Female	9 (19.6%)
Duration of disease (year) mean±SD	11.17±5.05
Dominant site of symptom (%)	
Right	38 (82.6%)
Left	8 (17.4%)
Pharmacologic treatment (%)	
L-dopa	44 (95.6%)
Amantadine	33 (71.7%)
NO. of electrodes mean±SD	
Right	3.60±0.98
Left	3.44±1.08

Table 1. Baseline and demographic variables in the PD patients.

Statistical Analysis: The data was analyzed using SPSS v.16 software for windows (Chicago IL, USA). In descriptive analysis the parameters such as frequency, mean and standard deviation (SD) were reported. Moreover, the coefficients of variations (CV) were calculated for each distance in order to evaluate and compare the variation of each distance with the others. The higher CV was the more variation of was existed for the distance. The analytical procedures were performed using statistical tests. Independent sample T-test was performed to evaluate the significancy of the differences in the mean of distance values regarding qualitative variables of the study (such as sex and age groups). In addition one sample T-test was used to compare the mean values of different distances in our study with finding of others.

A 5 percent probability of a type I error (two-tailed), and a power of 80 percent were considered in the analysis. All reported P-values were two-tailed and a P-value of <0.05 was considered to be significant.

Results

Baseline characteristics: Forty six individuals with PD (92 subthalamic nucleuses) were recruited consecutively in this study. 37

	Distance	Minimum	Maximum	Mean	Std. Deviation
MCP	X	97.40	104.10	100.14	1.26
	Y	92.40	103.60	98.60	2.70
	Z	82.80	105.40	96.32	4.91
Right	X	86.50	93.50	89.066	1.54
	Y	90.00	106.00	95.87	3.18
	Z	84.50	111.50	100.16	5.45
Left	X	109.00	116.00	111.20	1.51
	Y	90.00	105.00	95.88	3.17
	Z	84.50	111.50	100.16	5.45

Table 2. A descriptive characteristic of the location of MCP and both sides of STN coordinates (All measurements are in mm).

(80.4%) were male and 9 (19.6%) female with the mean age of 49.93 (SD=8.95) yr ranges between 31 to 72 years old. The mean duration of PD was 11.17 (SD=5.05) yr ranges between 5 to 25 years. The most frequent symptom dominant site was right in 38 (82.6%) patients. All baseline and demographic variables of the patients are listed in Table 1.

MRI anatomical parameters: After performing DBS in the PD patients, the parameters such as target coordinates (X, Y, Z) and the distances from MCP to the center of STN in all three axes on both sides were measured by means of MRI targeting. The descriptive characteristics of the location of MCP and the both sides' (right and left) STN in X-, Y- and Z-coordinates are listed in Table 2. Also, Figures 1-3 shows the location of these measurments (MCP, right and left STN, respectively) in individuals who underwent DBS in our study.

After calculating the distance between the individual X-, Y- and Z-target coordinates with MCP position, the average locations of the clinically efficient contact of the chronic stimulating electrodes were obtained. As illustrated in Table 3, the mean value of X-coordinates of right and left STN referred to the MCP were 11.05 (SD=0.94) and 11.06 (SD=1.01) mm, respectively. The average locations of the efficient contacts of the electrodes in right and left STN were located at 3.19 (SD=1.08) and 3.17 (SD=1.10) mm in the Y-axis direction regarding the position of MCP, respectively. Moreover, the mean distance value of Z-coordinate of STN referred to the MCP was 3.68 (SD= 0.77) mm. As it is shown in Table 3, the coefficient of variation (CV) was also calculated for

	Distance	Minimum	Maximum	Mean	Std. Deviation	CV[a]
Right	X	9.10	13.70	11.05	.94	8.51
	Y	1.30	5.80	3.19	1.08	33.86
	Z	1.70	5.80	3.68	.77	20.92
Left	X	9.30	15.00	11.06	1.01	9.13
	Y	1.30	5.80	3.17	1.10	34.70
	Z	1.70	5.80	3.68	.77	20.92

[a] Coefficient of variation

Table 3. A descriptive characteristic of distances of STN coordinates referred to the MCP on both sides (All measurements are in mm).

Author	Number of localized STN	Lateral (relative to midline)	P-value	A-P (relative to midcommisural point	P-value	Vertical (relative to AC-PC plane	P-value
Starr et al [9]	76	11.8	<0.001*	2.4	<0.001*	3.8	0.515
Saint-Cyr et al [31]	58	11.72	<0.001*	1.62	<0.001*	2.47	<0.001*
Zonenshayn et al [28]	66	13.3 ± 2.3	<0.001*	2.1 ± 0.5	<0.001*	2.8 ± 0.1	<0.001*
Vergani et al [30]	50	10.10 ± 1.21	<0.001*	3.75 ± 1.51	0.002*	5.10 ± 1.50	<0.001*
Sanchez Castro et al [32]	-	12.57 ± 1.39	<0.001*	3.29 ± 1.36	0.540	3.16 ± 0.89	0.053
Lanotte et al [33]	28	11.6 ± 0.9	0.001*	2.7 ± 0.7	0.014*	3.8 ± 1.1	0.515
Hamid et al [21]	54	11.7 ± 1.3	<0.001*	2.1 ± 1.43	<0.001*	3.8 ± 1.22	0.515
Danish et al [29]	52	10 ± 0.7	<0.001*	0.7 ± 0.2	<0.001*	3.3 ± 0.9	0.207
Benabid et al [17]	52	11.98 ± 1.12	<0.001*	5.02 ± 0.71	<0.001*	1.5 ± 0.66	<0.001*
Andrade-Souza et al [34]	28	12.12 ± 1.45	<0.001*	2.41 ± 1.63	<0.001*	2.39 ± 1.49	<0.001*
Pollo et al [35]	62	12.04 ± 1.62	<0.001*	2.34 ± 1.63	<0.001*	2.57 ± 1.68	<0.001*
Present study	92	11.05 ± 0.94	-	3.19 ± 1.08	-	3.68 ± 0.77	-

* Statistical significant difference using one sample T-test

Table 4. The comparison of mean distance of the STNs from MCP in different studies with our findings.

each distance. The least variation was observed in the location of X-coordinate of right STN with the lowest CV of 8.51; whereas, the most variation seen in the location of Y-coordinate of left STN with the highest CV of 34.70.

More analysis was performed to find out the factors affecting these distances in PD patients. The results of independent sample T-test showed that the distance of STN from MCP in the Y-axis direction was significantly lower in PD patients who aged >50 years in both right [2.78 (SD=1.00) mm vs. 3.50 (SD=1.07) mm, P=0.039] and left [2.76 (SD=1.04) mm vs. 3.50 (SD=1.07) mm, P=0.034] sides. In contrast, there were not any significant difference in any location of STN between men and women (all P-values >0.05). Moreover, duration of disease did not have any relation with these distances (all P-values >0.05).

Disscusion

Using MRI targeting method, the results of our study revealed some informations about the average location for the clinically efficient contact of the chronic stimulating electrodes in the STN, at different directions and referred to MCP for Iranian PD patients underwent DBS. These finding lead to a considerable set of information which could help neurosurgens during DBS procedure in Iranian patients.

Unfortunately, it is difficult to locate the STN using traditional techniques due to its small dimensions and anatomical characteristics [20]. As a results,the knowledge of the mean distances of STN and also its' individual variation (like what we have found in our study) can potentially be useful for a better placement of electrodes during DBS surgery in order to have clinically more efficient contact of the chronic stimulating electrodes.

Until now, various methods have been used to localize the STN. One method involves using MRI to localize the STN [21]. The STN may directly visualised by T2 weighted coronal MRI sections, even though this technique may be affected by the typical MRI distorsion that influences stereotactic precision [22].

The STN may also be localized by an indirect procedure following a stereotactic atlas, calculating its position through the distance from the AC-PC line. Ventriculography may be used In order to correct the identification of both AC and PC and, probably, this is the most reliable procedure for the anatomical targeting of STN [23-25]. But a recent choice of depicted image of fusion in standard MRI sections and CT could show better anatomical detail in MRI and the better geometric precision inth CT SCAN [26]. MRI technology has advanced such that direct stereotactic imaging of the STN is no longer thought to be impractical and/or imprecise. The development of powerful stereotactic

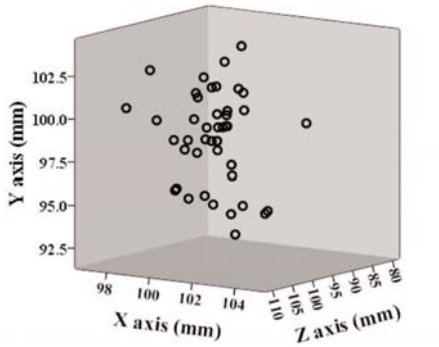

Fig. 1. The position id MCP values for three coordinates in the study group of PD patients.

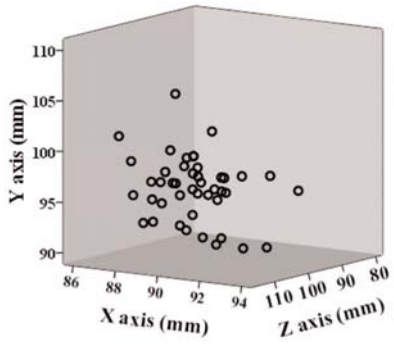

Fig. 2. The position of right STN values for three coordinates in the study group of PD patients.

computing resources has broadened stereotactic indications and facilitated their application [18, 27].

Regardless of the method of localization, some studies have evaluated the position of STN referred to MCP in different study population. For the first time in Iranian PD patients, we estimated this location by a site with 11 mm lateral, 3 mm inferior and 3mm posterior to the midcommissural point. In a similar study by Hamid et al in UK [21] the initial target point was localized at 12 mm lateral, 3mm posterior, and 4 mm inferior to the AC-PC midpoint by using direct visualisation of the STN in 42 lead placements through MRI. As compared, these results are approximately similar to our findings; whereas, some other studies had a different and various sets of distances.

Mean coordinates for active contacts reported by other authors are listed in Table 4. In addition, the results of one sample T-test to evaluate the significancy of the difference between their results and our findings are also listed. Considering all the data from different authors, our values for lateral location of STN appear to be between the mean coordinates of active contacts reported by Zonenshayn et al [28] and the mean coordinates reported by Danish et al [29] and Vergani et al [30]. Despite slight differences in mean coordinates values, active contacts appeared to be clustered in the same region.

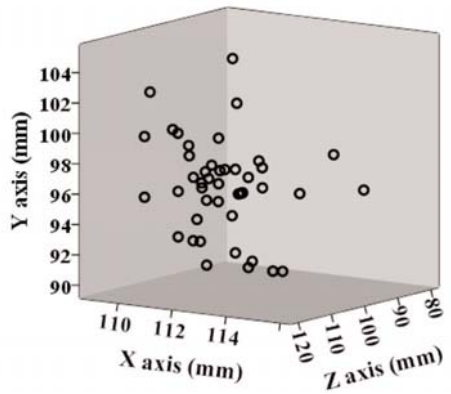

Fig. 3. The position of left STN values for three coordinates in the study group of PD patients.

Although AC-PC referential-based method shows an acceptable performance, its estimation needs AC and PC identification points by an expert and does not take into account interpatient variability, which is a very important factor.

In our study, the mean distances between the position of the STN and midcommissural point (MCP) was identified in an Iranian population of the PD patients by 3-dimentional MRI image targeting. This is estimated by a site of 11 mm lateral, 3 mm inferior and 3 mm posterior to the midcommissural point. In addition higher sample size of our study in comparison with most other similar studies has revealed a relationship between patients'age group and localization of STN in Y-axis direction as a unique finding. It seems that age-related degenerative changes of brain may have important role to ex-

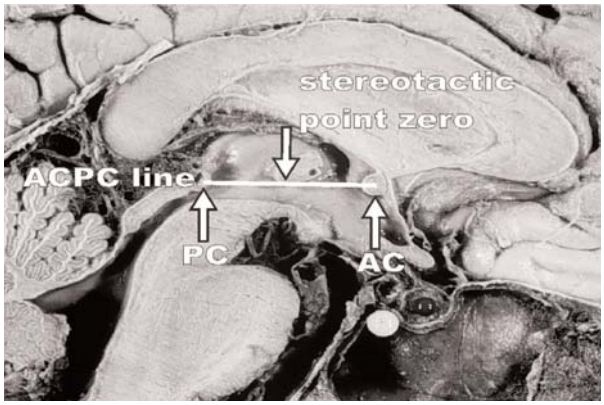

Fig. 4. Medial view on a bisected cadaver brain. The ACPC line is defined as the intercommissural line connecting the centers of anterior commissure (AC) and posterior commissure (PC)(36).

plain this finding and these changes may be due to the atrophy of brain parenchyma following longer history of the Parkinson's disease in this study. As a result, a lower distance was found in older PD patients. According to data presented in Table 4, one of the shortest lateral distances of STN from MCP are reported by Vergani et al [30] in a study with the mean age of 59.5 yr for the patients which is considerably much older than ours (49.9 yr). In another study by Zonenshayn et al [28], PD patients with the mean age of 56 yr were evaluated and the relative short A-P and vertical distances of STN were reported (2.1 and 2.8, respectively); whereas, these distances were significantly longer in our study with a less aged study population. These comparisons provided more evidences on the probable effect of patients' age on STN distances from MCP during DBS.

Conclusion

Although more direct studies are necessary to find the best point for stimulation, however, advances in imaging and computer technology have much to offer for stereotactic surgery. Despite the differences observed between various population of the PD patients in different studies, our results further emphasize the clustration of active contact points in same region. However, it is necessary to estimate the location of STN in different population in order to have a better placement of electrodes during DBS surgery.

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