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The association between surgical characteristics and cognitive decline following deep brain stimulation of the subthalamic nucleus in Parkinson's disease

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ABSTRACT

Objective: Despite optimal improvement in motor functioning, both short- and long-term studies have reported small but consistent changes in cognitive functioning following STN-DBS in Parkinson's disease (PD). The aim of the present study was to explore whether surgical characteristics were associated with cognitive decline one year following STN-DBS.

Methods: We retrospectively analyzed 49 PD patients who underwent bilateral STN-DBS. Cognitive change scores were related to the number of microelectrode recording (MER) trajectories, the STN length as measured by MER, and cortical entry points. Regression analyses were corrected for age at surgery, disease duration, education and preoperative levodopa responsiveness. Patients were then divided into a cognitive and non-cognitive decline group for each neuropsychological test and compared regarding demographic and surgical characteristics.

Results: One year postoperatively, significant declines were found in verbal fluency, Stroop Color-Word test and Trail Making Test B (TMT-B). Only changes in TMT-B were associated with the coronal entry point in the right hemisphere. The number of MER trajectories and STN length were not associated with cognitive change scores. When comparing the cognitive decline and non-cognitive decline groups, no significant differences were found in surgical characteristics.

Conclusions: The electrode passage through the right prefrontal lobe may contribute to subtle changes in executive function. However, only few patients showed clinically relevant cognitive decline. The use of multiple MER trajectories and a longer STN length were not associated with cognitive decline one year following surgery. From a cognitive point of view, DBS may be considered a relatively safe procedure.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective and widely accepted treatment for Parkinson's disease (PD), and associated with improved motor functioning and quality of life [1,2]. However, both short-term and long-term follow-up studies have reported small but reliable changes in cognitive functioning, especially in the executive function domain [3–7]. Several patient inherent characteristics have been associated with cognitive decline following STN-DBS, such as higher age, levodopa dosage, impaired attention, and axial symptoms [8,9]. Moreover, stimulation and surgical factors such as the location of the active electrode, the volume of tissue activated, and stimulation settings may partially explain changes in cognitive functioning [10–13]. It has also been suggested that cognitive decline

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following STN-DBS reflects a microlesion effect due to the trajectories used during surgery, such as trajectories intersecting the caudate nuclei [4,12,14–18].

Accurate placement of the electrode within the dorsolateral sensorimotor part of the STN is considered necessary for satisfactory outcome. To date, microelectrode recording (MER) is typically used to accurately detect the STN and to optimize lead implantation. A recent study showed that multiple simultaneously inserted microelectrodes may provide better guidance than single sequential microelectrodes [19]. Moreover, prefrontal entry points are ideally chosen in order to maximize the length of the DBS electrode within the STN, thereby offering more contact combinations for postoperative DBS programming [20,21]. However, it has been hypothesized that a greater number of MER trajectories could result in a greater degree of local injury, presumably through damage to functional areas along the trajectory or at the target site important for cognitive functioning, thereby contributing to cognitive decline following surgery [14,16,22]. Moreover, maximizing the STN's length may increase the chance of affecting the STN's associative area, hence leading to cognitive decline [16].

The goal of the present study was to investigate whether characteristics of the surgical trajectory, including the number of MER trajectories, the STN length as measured by MER, and the angles (cortical entry points) of the lead trajectories, are associated with cognitive decline one year following STN-DBS in PD patients. Furthermore, we tested associations between these characteristics and motor improvement one year following surgery. The results may help in optimizing the surgical procedure by balancing the benefits and the disadvantages to attempt for maximal STN length.

2. Material and methods

2.1. Design and participants

This study was conducted at Maastricht University Medical Centre and was exempted from ethical approval by the local ethical committee (METC azm/UM). Informed consent was not obtained from the patients because of the retrospective nature of the study. All patients (N = 81) who underwent bilateral STN-DBS for Parkinson's disease between 2005 and March 2017 were retrospectively identified (see Appendices Table A1). Inclusion criteria for our study were: [1] pre- and post-operative neuroimaging sufficient for determining the surgical trajectory [2], MER recordings [3], available pre- and one year post-neuropsychological assessment, and [4] no complications or re-implantation of electrodes. A total of 49 patients were found eligible for the study (see Appendices Table A2 for reasons for exclusion), of which 20 patients were also included in an earlier study [12].

2.2. Surgical details

The surgical procedure has been described in detail previously [23] and included direct targeting of the STN and MER guidance during surgery. Trajectory planning was performed on gadolinium enhanced T1 images using dedicated surgical planning software (Framelink, Medtronic, Minneapolis, USA). The length of the inter-commissural line (AC-PC line), coordinates with respect to mid-commissural point (MCP) and both sagittal and coronal angles of the trajectory were assessed by a neurosurgeon. When applicable, up to five MER trajectories per side were used. In case of the presence of vessels, the respective trajectories were discarded. MER were initiated 10 mm above the target point and continued with 1.0 mm steps. From 5 mm above target, steps of 0.25−0.50 mm were used for MER until STN activity disappeared and/or until the typical substantia nigra activity appeared, as assessed by a clinical neurophysiologist. Trajectories with the longest STN activity were chosen for test stimulation. The trajectory with the least side effects and highest effect on the key symptom with largest stimulation window (amplitude threshold of therapeutic and side-effects) was chosen for the placement of the final electrode. The length of this final trajectory as measured by MER was recorded in mm (STN length).

2.3. MRI analysis

All patients had a postoperative CT or MRI (43 %) scan for evaluation of postoperative complications and electrode localisation. Pre-and postoperative images were imported into the Framelink 5.1™ (Medronic BV, Minneapolis HQ, USA) software. After orientation of the data set had been confirmed, the pre-operative MRI was automatically fused with the postoperative MRI or CT for analysis of the postoperative surgical trajectory. Subsequently, a neurosurgeon created linear vectors between the observed lead tip and cortical entry point in multiplanar and probe's eye view of all 98 DBS electrode trajectories (both hemispheres in each patient) and determined the coronal and sagittal angles of the entry points. For the coronal entry point (named mid-sagittal plane in the software), angles closer to 0° were located to the midpoint of the AC-PC line, while angles close to 90° were located laterally. For the sagittal entry point (named axial plane in the software) angles closer to 0° were closer to the midpoint of the AC-PC line, and angles closer to 90° were located dorsally.

2.4. Neuropsychological and motor assessment

Neuropsychological assessment was performed one month before surgery and one year after surgery. Preoperatively, patients were tested with medication 'ON', and postoperatively with both medication and stimulation 'ON'. The tests were part of the standard protocol for PD patients receiving STN-DBS. If available, alternating forms were used at follow-up time points to minimize practice effects. For the current study, we selected the Auditory Verbal Learning Test (AVLT) immediate and delayed recall [24]. The category (animals and professions) and letter fluency test were used as measures of semantic and phonemic verbal fluency, respectively [25]. The Stroop Color-Word Test was used to measure mental speed and response inhibition [26]. The Trail Making Test (TMT) (part A and B) were used to assess mental speed and cognitive flexibility, respectively [27].

Motor state was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) part III. Preoperatively, patients were tested in 'on' and 'off' medication state, while postoperatively assessments were performed with stimulation and medication 'on'. Percentage improvement in motor disability was determined in respect of the preoperative off-medication condition.

2.5. Statistics

Statistical analyses were performed using IBM SPSS Statistics 25.0 [28]. Possible differences in STN length, cortical entry points and number of MER trajectories between the right and left hemisphere were analysed using paired sample *t*-test. Changes in clinical and neuropsychological variables following DBS were analysed using parametric *t*-test statistics and non-parametric Wilcoxon-Rank order tests when appropriate (lack of normal distribution of data). A p-value <0.05 was considered to be statistically significant. No correction for multiple comparisons was applied in order to reduce the risk of type II error given the importance of detecting any adverse effects of surgery. Statistically significant mean differences underwent Cohen's d calculation for effect size.

Multiple regression analyses were performed to analyse the associations between surgical characteristics and both cognitive decline and motor improvement one year following surgery. The dependent variables were raw change scores of the neuropsychological tests that showed a statistically significant decline following surgery and the percentage of UPDRS III improvement, respectively. The predictor variables were the surgical characteristics, each tested in a separate model for both left and right hemisphere, and adjusted for age, education,

disease duration and Levodopa equivalent daily dose (LEDD) at baseline. For the regression analyses, a Bonferroni adjusted p-value < 0.001 was considered statistically significant.

Lastly, for each neuropsychological test that showed statistically significant change following surgery, patients were categorized into two distinct groups based on the presence or absence of cognitive decline: the cognitive decline group and the non-cognitive decline group (or stable performers). For this purpose, standardized Z-score were calculated at baseline and follow-up based on the mean and standard deviation of the total sample at baseline. Cognitive decline was defined as a raw score change (decline for verbal fluency and AVLT, and increase for TMT, Stoop Color-Word test) >1 Z-score from baseline. Groups (cognitive decline yes / no) were then compared using non-parametric Mann-Whitney tests for demographic and surgical characteristics. For the comparison analyses, a Bonferroni adjusted p-value < 0.002 was considered statistically significant.

3. Results

3.1. Patient and surgical characteristics

The study population consisted of 31 males and 18 females. The average age at of PD onset was 49.0 years (SD = 9.6) and the average age at DBS surgery was 60.1 years (SD = 8.5). The average disease duration was 133.7 months (SD = 31.7). Mean UPDRS part III score at baseline was 37.7 (12.0) and the average LEDD was 1346.1 mg (SD = 329.9).

Surgical characteristics are provided in Table 1. In 32 patients the right hemisphere was operated first because of left side dominant PD symptoms. The average STN length was 5.2 mm (SD = 1.5), the mean sagittal angle was 56.6 degrees (SD = 8.9) and the mean coronal angle was 23.3 degrees (SD = 5.1). There were no statistically significant differences between the right and left hemispheres regarding STN length, sagittal and coronal angle (coronal entry points) and number of MER trajectories.

Table 1
Surgical characteristics.

	Right hemisphere (N)	Left hemisphere(N)	Total (N)	
MER trajectories*				
- 1	0	0	0	
- 2	3	1	4	
- 3	14	17	31	
- 4	21	24	45	
- 5	10	6	16	
Chosen trajectory**				
- anterior	4	4	8	
- medial	6	3	9	
- central	29	34	63	
- lateral	5	5	10	
- posterior	3	2	5	
First side operation	32	17		
	Right	Left	Total	P value
STN length	5.1 (1.5)	5.3 (1.4)	5.2 (1.5)	0.25
Sagittal angle	56.3 (8.9)	56.9 (9.1)	56.6 (8.9)	0.45
Coronal angle	23.3 (5.1)	23.7 (5.0)	23.5 (5.0)	0.67
MER trajectories (median, range)*	4 (2–5)	4 (2–5)	4 (2–5)	0.52

MER trajectories: number of electrodes used for microelectrode recording registration, STN = subthalamic nucleus.
Results are presented as means and standard deviations, unless otherwise specified.
* Data missing for 1 patient.
** Data missing for 1 patient bilaterally and for 1 patient unilaterally.

3.2. Neuropsychological and motor outcome following STN-DBS

One year following surgery there were statistically significant changes in Stroop Color-Word test performance (medium effect size), in TMT-B performance (small effect size) and in both category and letter fluency performance (large effect size) (Table 2). All changes reflect a decline in cognitive functioning. LEDD decreased by 54 % and UPDRS part III improved by 50.1 % (Table 3), all on a group level.

3.3. Associations between surgical characteristics and both cognitive decline and motor improvement

Multiple regression analyses were run to test the associations between surgical characteristics and cognitive decline (each tested in a separate model), age, education, disease-duration and LEDD at baseline. Changes in TMT-B performance were statistically significantly associated with right coronal angle: $F(5,37) = 5.975$, $p < 0.00125$, R [2] = 0.447, and only right coronal angle added statistically significantly to the model: $p < 0.00125$. The surgical characteristics were not associated with changes in any of the other neuropsychological tests, nor with improvement in UPDRS III scores.

3.4. Cognitive decline

Patients were categorised into a cognitive decline or non-cognitive decline group for each neuropsychological test separately (see Table 4). Patients with cognitive decline in Stroop Color-Word (card III) performance had a higher age at surgery ($p = 0.001$), compared to patients without cognitive decline. For the other neuropsychological tests, there were no statistically significant differences between the cognitive decline and non-cognitive decline groups.

4. Discussion

In this retrospective study we investigated whether characteristics of the surgical trajectory, including the number of MER trajectories, the

Table 2
Neuropsychological test scores at baseline, 1 year following DBS surgery and test change scores (T1 minus T0). Means, standard deviations and Wilcoxen signed rank analyses or T test are shown.

	N	Baseline	1 year follow up	Change score	P-value	Cohen's d
Stroop I	49	51.0 (12.0)	55.6 (15.8)	4.6 (8.5)	0.000	0.54
Stroop II	49	66.9 (15.1)	76.7 (25.1)	9.8 (16.4)	0.000	0.60
Stroop III	48	113.4 (38.8)	143.4 (82.5)	29.8 (64.1)	0.000	0.46
Stroop Int	48	50.1 (32.3	74.1 (69.9)	24.1 (59.1)	0.000	0.41
TMT A	46	39.8 (15.0)	42.4 (18.6)	1.8 (12.4)	0.46	
TMT B	45	104.0 (69.2)	116.8 (76.7)	12.8 (41.9)	0.047	0.31
AVLT total	48	43.5 (10.9)	43.9 (10.7)	0.4 (2.9)	0.69	
AVLT recall	48	8.7 (3.2)	8.4 (3.2)	−.33 (2.9)	0.43	
Fluency category	49	41.3 (9.8)	33.9 (11.5)	−7.4 (8.4)	0.000	0.89
- animals		23.8 (5.2)	19.5 (6.5)	−4.3 (5.0)	0.000	0.86
- occupations		18.0 (5.5)	14.8 (5.6)	−3.2 (4.2)	0.000	0.76
Fluency letters	48	34.3 (11.4)	29.8 (12.3)	−4.6 (8.2)	0.000	0.56

Stroop = Stroop Color-Word test, Int = interference score, TMT = Trail Making Test, AVLT = Auditory Verbal Learning test.

Table 3
UPDRS part III and LEDD scores at baseline and 1 year following DBS surgery and change scores. Means, standard deviations and T test analyses are shown.

	N	Baseline	1 year follow up	Change score	P-value
LEDD (mg/day)	47	1346.1 (629.9)	617.9 (476.5)	−728.2 (466.9)	<0.001
UPDRS III OFF	40	37.7 (12.5)	18.8 (9.8)	−18.9 (14.0)	<0.001
UPDRS III ON	41	19.3 (11.5)	18.4 (9.5)	−.94 (12.3)	0.63

Patients were scored post-operatively with stimulation and medication 'on'.
LEDD = levodopa equivalent daily dose, UPDRS = Unified Parkinson Disease Rating Scale, OFF = compared to baseline 'off' medication, ON = compared to baseline 'on' medication.

STN length as measured by MER and angles (cortical entry points) of the surgical trajectory, were associated with cognitive decline and motor improvement one year following STN-DBS in PD patients. One year postoperatively, we found significant declines in verbal fluency, Stroop Color-Word test and TMT-B. Changes in TMT-B were associated with the coronal entry point in the right hemisphere, independently of age, education, disease duration, and LEDD at baseline. When comparing patients with and without clinically relevant cognitive decline in TMT-B performance, no differences in any of the surgical characteristics could be found. Motor improvement was not associated with characteristics of the surgical trajectories.

The declines as found in tests that measure executive function are consistent with other reports on cognitive (side)effects of STN-DBS [29]. Similar to previous studies [10,14] the number of MER trajectories used for accurate lead placement was not associated with cognitive decline one year after surgery. Moreover, no associations were found between STN length as measured by MER and cognitive or motor outcome, respectively, which is in line with previous studies [16,30,31]. Although these results cannot exclude a transient microlesion effect as proposed by others [22], these findings suggest that there is no increased risk for cognitive decline at one year following surgery when increasing the number of MER trajectories or with maximizing the STN length.

Changes in TMT-B performance, though showing a small effect size, were associated with the cortical entry point in the right hemisphere only, whereas we found no association between the left hemisphere and changes in TMT-B performance. Interestingly, several other studies observed hemispheric differences when studying the relationship between the lead trajectories and cognitive decline [10,11,16]. La Goff and colleagues (2015), for example, found that patients with a decline in semantic verbal fluency had a left trajectory with a more anterior cortical entry point [16], while the present study did not find any relationship between cortical entry points and decline in verbal fluency performance. Changes in both semantic and phonemic verbal fluency following surgery, with moderate to large effect sizes, are one of the most common and robust findings in the literature [4,22,32–34], and there have been inconsistent findings regarding the associations between changes in verbal fluency performance following DBS and the electrode trajectories. Tröster and colleagues (2017) found differences between the effect of surgery and stimulation on semantic and phonemic fluency, respectively, suggesting that only semantic fluency is affected by the lead trajectory [18]. On the contrary, Okun and colleagues (2012) proposed that phonemic verbal fluency was the result of the lead placement, because a similar degree of decline was observed in both on-stimulation and off-stimulation states [35]. Another study demonstrated microstructural injuries along the electrode trajectories in white matter bundles that are implicated in verbal fluency following STN-DBS [15].

In general, executive function tests such as verbal fluency and TMT-B are difficult to interpret as they rely on a variety of cognitive processes. Semantic and phonemic verbal fluency depend on shared and distinct distributed brain regions, including the left inferior frontal gyrus, anterior cingulate gyrus, left frontal regions and temporal networks [15]. Performance on TMT-B involves divided and visual attention, cognitive flexibility, speed of processing, set-shifting and working memory, which are most likely mediated by widespread activation of the bilateral PFC, as well as dorsomedial and dorsolateral regions [36–39]. As such, the findings in the present study could be regarded as non-specific to these numerous aspects of executive functioning. Importantly, the association between the right coronal entry point and TMT-B is based on changes in neuropsychological test performance and does not necessarily translate into impairment in daily activities. Only five out of 45 patients showed clinically relevant decline in TMT-B performance, and these five patients did not differ in terms of surgical characteristics compared to the non-decline group. Though, based on the findings of Costentin and colleagues [15] for verbal fluency, it would be interesting to know whether the decline in TMT-B performance correlates with damage of specific fiber pathways, in particular in the right

Table 4
Comparisons of demographic and surgical factors between the cognitive decline vs the non-cognitive decline group in Stroop Color-Word test III performance, TMT-B performance and verbal fluency. Means, standard deviations and Mann-Whitney test analyses are shown.

	Stroop III			TMT-B			Fluency category			Fluency letters		
	Yes	No	P	Yes	No	P	Yes	No	P	Yes	No	p
N	5	44		5	40		8	41		9	39	
Age at surgery	71.0 (2.4)	59.1 (8.0)	**0.001**	69.0 (8.4)	58.6 (6.0)	0.011	65.0 (8.8)	59.1 (8.2)	0.09	60.8 (10.8)	59.7 (8.1)	0.68
Disease duration	100.8 (79.9)	138.7 (59.7)	0.10	117.6 (116.8)	132.0 (55.9)	0.13	123.0 (40.4)	135.8 (65.5)	0.66	154.7 (85.8)	127.4 (55.4)	0.50
LEDD (mg/day)	711.6 (489.6)	1432.5 (609.0)	0.013	687.0 (450.8)	1416.4 (621.0)	0.010	1338.5 (822.3)	1347.6 (596.4)	0.79	1297.8 (459.8)	1352.7 (677.0)	0.85
Education (range)	4.6 (3–6)	5.2 (2–7)	0.10	4.6 (3–6)	5.2 (2–7)	0.37	5.1 (3–6)	5.1 (2–7)	0.97	5.0 (4–7)	5.2 (2–7)	0.50
Right												
MER trajectories (range)	3.8 (3–5)	3.8 (2–5)	0.41	3.3 (3–4)	3.8 (2–5)	0.19	3.8 (2–5)	3.8 (2–5)	0.97	3.8 (2–5)	3.8 (2–5)	0.99
STN length	4.1 (2.3)	5.1 (1.3)	0.41	4.0 (2.2)	5.2 (1.4)	0.33	(5.3) (1.0)	5.0 (1.5)	0.99	4.7 (1.4)	5.2 (1.4)	0.45
Sagittal angle	58.8 (9.7)	56.0 (9.5)	0.53	59.2 (9.3)	56.8 (8.7)	0.54	57.6 (11.8)	56.0 (8.2)	0.64	52.8 (4.8)	56.9 (9.4)	0.23
Coronal angle	28.5 (4.8)	22.9 (4.9)	0.025	28.8 (4.3)	22.7 (4.6)	0.007	23.6 (6.3)	23.3 (5.0)	0.84	22.2 (7.2)	23.8 (4.6)	0.26
Left												
MER trajectories (range)	3.5 (3–4)	3.8 (2–5)	0.13	3.5 (3–4)	3.8 (2–5)	0.57	4.0 (3–5)	3.7 (2–5)	0.25	3.9 (3–5)	3.7 (2–5)	0.60
STN length	4.1 (2.1)	5.4 (1.3)	0.13	4.1 (2.2)	5.5 (1.2)	0.11	5.5 (1.7)	5.2 (1.4)	0.52	4.8 (1.6)	5.4 (1.4)	0.32
Sagittal angle	59.7 (6.5)	56.6 (9.5)	0.36	59.9 (6.5)	56.8 (9.8)	0.34	57.3 (13.4)	56.8 (8.3)	0.62	57.8 (4.7)	56.7 (10.0)	0.48
Coronal angle	23.0 (5.0)	23.8 (5.1)	0.77	24.3 (5.2)	23.8 (4.7)	0.88	26.1 (6.9)	23.2 (4.5)	0.23	23.7 (3.6)	23.7 (5.3)	0.76

Stroop = Stroop Color-Word test part III, TMT = Trail Making Test, LEDD = levodopa equivalent daily dose, MER trajectories = number of electrodes used for microelectrode recording registration.

hemisphere. This information is not available for the present sample but would be helpful to determine the optimal cortical entry points in terms of cognitive safety.

The literature so far shows inconsistent results with respect to the surgical impact on cognition. This inconsistency is due to many methodological differences, including differences in follow-up period, definitions of decline and assessment, but overall the sample sizes are relatively small, including the present study. Besides these methodological issues, changes in cognitive functioning rely upon a complex interplay of numerous factors, including age, levodopa-response, disease-duration and -progression, stimulation factors, pre-operative motor symptoms, preoperative cognitive functioning and morphometric measures of brain atrophy [8,40], which can hardly be examined in one study. Further effort should be put in data sharing and multicenter studies to increase sample sizes and thereby overall power. Additionally, study designs with neuropsychological assessment in medication-ON, and both stimulation ON and OFF condition, may exclude (or demonstrate) a stimulation effect and, as such, relieve some pressure of the power.

5. Conclusion

The electrode passage through the right prefrontal lobe may contribute to subtle changes in executive function. However, only few patients showed clinically relevant cognitive decline and as such the impact is low. More importantly, while the use of multiple MER trajectories and a longer STN length were not associated with cognitive decline one year following surgery, we were also not able to observe a gain in motor improvement when using multiple MER trajectories and a longer STN length. To conclude, from a cognitive point of view, DBS can be considered a relatively safe procedure. Surgical teams that are ambitious of maximizing the length of the DBS electrode within the STN do not have to be restrained by a risk of cognitive side effects, but still have to prove its clinical benefits.

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CRediT authorship contribution statement

Anne E.P. Mulders: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft. **Yasin Temel:** Conceptualization, Data curation, Writing - review & editing. **Mehmet Tonge:** Investigation. **Frédéric L.W.V.J. Schaper:** Investigation. **Vivianne van Kranen-Mastenbroek:** Data curation, Writing - review & editing. **Linda Ackermans:** Validation, Writing - review & editing. **Pieter Kubben:** Validation, Writing - review & editing. **Marcus L.F. Janssen:** Data curation, Writing - review & editing. **Annelien Duits:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.106341.

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