The role of dominant striatum in language: a study using intraoperative electrical stimulations

S Gil Robles, P Gatignol, L Capelle, M-C Mitchell, H Duffau


Background: The role of the striatum in language remains poorly understood. Intraoperative electrical stimulation during surgery for tumours involving the caudate nucleus or putamen in the dominant hemisphere might be illuminating.

Objectives: To study the role of these structures in language, with the aim of avoiding postoperative definitive aphasia.

Methods: 11 patients with cortico-subcortical low grade gliomas were operated on while awake, and striatal functional mapping was done. Intraoperative direct electrical stimulation was used while the patients carried out motor and naming tasks during the resection.

Results: In five cases of glioma involving the dominant putamen, stimulations induced anarthria, while in six cases of glioma involving the dominant caudate, stimulations elicited perseveration. There was no motor effect. The striatum was systematically preserved. Postoperatively, all patients except one had transient dysphasia which resolved within three months.

Conclusions: There appear to be two separate basal ganglia systems in language, one mediated by the putamen which might have a motor role, and one by the caudate which might have a role in cognitive control. These findings could have implications for surgical strategy in lesions involving the dominant striatum.

METHODS

Subjects
Among a series of 100 patients operated on under local anaesthesia at the Salpêtrière Hospital between 1996 and 2003 for a low grade glioma affecting the language regions, we selected 11 in whom surgical resection involved the dominant striatum.

Preoperatively, all patients had a neurological examination. Language was tested using a French standardised adaptation of the Boston diagnostic aphasia examination (BDAE). Hemispheric dominance was defined using a standardised neuropsychological questionnaire. The topography of the tumour was accurately analysed on preoperative magnetic resonance imaging (MRI; T1 weighted and spoiled gradient images obtained before and after gadolinium enhancement in the three orthogonal planes, T2, and FLAIR weighted axial images).

Intraoperative mapping
The 11 patients underwent surgery under local anaesthesia so that functional cortical and subcortical mapping could be carried out using direct brain stimulations. This method, including the electrical parameters and the intraoperative clinical tasks, has been described by us previously. Briefly, a bipolar electrode with 5 mm spaced tips delivering a biphasic current (pulse frequency 60 Hz; single pulse phase duration 1 ms; amplitude 2 to 8 mA) (Ojemann cortical stimulator I, Radionics Inc, Burlington, Massachusetts, USA) was applied on the brain of conscious patients. No neuronavigation system was used, because of the risk of brain shift in this type of voluminous tumour. We preferred to use a real time
ultrasonographic system so as not only to delineate the tumour before its removal but also to identify residual tumour along the resection plane.

In a first stage, cortical mapping was carried out before any resection, in order to avoid damage to eloquent areas. Sensorimotor mapping was done first, to confirm a positive response—for example, the induction of movement or paraesthesiae in the contralateral hemibody when the primary sensorimotor areas were stimulated in a patient at rest. The patient was then asked to count (in order from 1 to 10, and so on) and to name pictures (preceded by “this is a...”), so as to map the cortical language sites known to be inhibited by electrical stimulation using the parameters described above. For the naming task, we used the DO 80, which consists of 80 black and white pictures selected according to variables such as frequency, familiarity, age of acquisition, and level of education. The patient was never informed when the brain was stimulated. The duration of each stimulation was four seconds. At least one picture presentation without stimulation separated each stimulation, and no site was stimulated twice in succession, to avoid seizures. Each cortical site (size 5 x 5 mm, determined by the spatial resolution of the probe) of the whole cortex exposed by the bone flap was tested three times. It is nowadays accepted, since the seminal publication of Ojemann et al., that three tasks are sufficient to assess whether a cortical site is essential or non-essential for language, as determined by the generation of speech disturbances during three stimulations, with normalisation of language as soon as the stimulation is stopped. It should be noted that this limitation of the number of trials takes account of the time limitation imposed by the surgical procedure because the patient is awake. The type of language disturbance was defined by a speech therapist who was present in the operative room during the functional mapping. Each eloquent area was marked using a sterile number tag on the brain surface, and its location was correlated with the anatomical landmarks (sulci, gyri, tumour boundaries) previously identified by ultrasonography.

During a second surgical stage, the tumour was removed, with alternating resection and subcortical stimulation. The functional pathways were followed progressively from the cortical eloquent sites already mapped to the full depth of the resection as far as the striatum, which was stimulated in all 11 patients using the same methodology. The patient was asked to continue to carry out both motor tasks (repeated opening and closing of the non-dominant hand) and language tasks (picture naming) when the resection approached the subcortical language structures (white fibres and grey nuclei). These were identified by speech inhibition during stimulation in the same way as at the cortical level. To achieve the optimum tumour removal consistent with preservation of functional areas, all resections were continued until eloquent structures were encountered around the surgical cavity, and were then terminated along functional boundaries.

The postoperative neurological outcome was assessed systematically immediately after the operation and at three months, using the same language tasks as were used preoperatively. A control MRI examination was carried out in all cases, immediately after surgery and at three months. This imaging allowed us first to evaluate the quality of the glioma removal, and second to analyse where the resection had stopped in relation to the location of the striatum.

RESULTS

The clinical, radiological, and surgical characteristics of the 11 patients are summarised in table 1.

Clinical presentation

The series consisted of eight men and three women, ranging in age from 25 to 52 years. Nine patients were right handed (four with a score of +100, five with a score of +90), and two were left handed (−80). The presenting symptoms were partial seizures with transient language disturbances in four cases, and generalised seizures in seven. Preoperative neurological testing was normal except for a moderate cognitive disorder in patient 3 and slight dysarthria in patient 5. There was no other language disorder involving spontaneous speech, auditory comprehension, word generation, naming, repetition, reading, or writing, according to the BDAE criteria.

Preoperative MRI

All the tumours appeared as T1 weighted hypointense and T2/FLAIR weighted hyperintense lesion, without enhancement after gadolinium administration.

The 11 tumours were located in the dominant hemisphere—that is, nine on the left side, and two on the right (in the left handed patients). Five lesions were invading the left insular lobe with involvement of the extrema capsule, the claustrum, and the external capsule up to the putamen (patients 1, 2, 3, 4, and 5) (fig 1A). Six tumours were invading the frontomesial precentral structures, with involvement of the subcortical pathways up to the head of the caudate nucleus—four left sided lesions (in patients 6, 8, 9, and 10) (fig 2A), and two right sided (in patients 7 and 11).

Operative findings

The surgical procedure under local anaesthesia was well tolerated by all 11 patients. In all cases, language structures were clearly identified. The results of the striatal mapping differed according to the subregion stimulated.

Insular lesions

Cortical mapping over the insular cortex showed no response, while stimulation of the frontal operculum elicited speech arrest in all five patients (and also during stimulation of the superior temporal gyrus in two cases). Following insular resection, stimulation of the deep white matter in the posterior part of the cavity induced dysarthria in four cases and anomia in one. More anteriorly, when the resection in the depth of the cavity came into contact with the grey nuclei, which were easily identified because of the change in tissue colour, texture, and vasculature in comparison with the white matter, electrical stimulation of the lateral part of the anterior lentiform nucleus elicited a clear anaesthesia in all five patients; they were totally unable to articulate, or even to generate the slightest phonation (fig 1B). This anaesthesia occurred systematically during each stimulation and resolved immediately at the end of stimulation. There was no disruption of motor function during stimulation of the lentiform nucleus, as the patient continued with regular opening and closing of the hand, and there was no facial contraction during the period of inability to articulate. Tumour removal was therefore systematically interrupted at this level.

Frontomesial precentral lesions

Cortical mapping allowed the identification of naming sites within the premotor areas in all six patients. Stimulation of the corresponding subcortical fibres during the resection also elicited anomia laterally (with motor responses posteriorly owing to stimulation of the pyramidal pathways). At the end of the resection, after opening the frontal horn of the ventricle, stimulation of the lateral wall of this horn—where the supero-medial part of the head of the caudate nucleus was clearly identifiable owing to its colour and
### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Preoperative neurological examination</th>
<th>Location of the lesion</th>
<th>Preoperative clinical findings</th>
<th>Stimulation site</th>
<th>Intraoperative findings: stimulation mapping</th>
<th>Immediate postoperative clinical results</th>
<th>Delayed postoperative clinical results (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Left insular glioma involving left insula</td>
<td>No worsening</td>
<td>Head of left caudate</td>
<td>Anarthria induced by stimulation of head of left caudate</td>
<td>No deficit; return to normal life</td>
<td>No deficit; return to normal life</td>
</tr>
<tr>
<td>2</td>
<td>Partial seizures</td>
<td>Left insular glioma involving left insula</td>
<td>Mild dysarthria</td>
<td>Head of left caudate</td>
<td>Anarthria induced by stimulation of head of left caudate</td>
<td>Recovery; return to normal life</td>
<td>Recovery; return to normal life</td>
</tr>
<tr>
<td>3</td>
<td>Partial seizures</td>
<td>Left insular glioma involving left insula</td>
<td>Speech slowness (partial dominant SMA syndrome) with perseveration</td>
<td>Head of left caudate</td>
<td>Anarthria induced by stimulation of head of left caudate</td>
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<tr>
<td>4</td>
<td>Partial seizures</td>
<td>Left insular glioma involving left insula</td>
<td>Perseveration induced by stimulation of superior part of head of caudate</td>
<td>Head of left caudate</td>
<td>Anarthria induced by stimulation of head of left caudate</td>
<td>Perseveration induced by stimulation of superior part of head of caudate</td>
<td>Perseveration induced by stimulation of superior part of head of caudate</td>
</tr>
<tr>
<td>5</td>
<td>Generalised seizures</td>
<td>Right insular glioma involving right insula</td>
<td>No worsening</td>
<td>Head of right caudate</td>
<td>Anarthria induced by stimulation of head of right caudate</td>
<td>No deficit; return to normal life</td>
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</tr>
<tr>
<td>6</td>
<td>Generalised seizures</td>
<td>Right insular glioma involving right insula</td>
<td>Mild dysarthria</td>
<td>Head of right caudate</td>
<td>Anarthria induced by stimulation of head of right caudate</td>
<td>Recovery; return to normal life</td>
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<tr>
<td>7</td>
<td>Generalised seizures</td>
<td>Right insular glioma involving right insula</td>
<td>Speech slowness (partial dominant SMA syndrome) with perseveration</td>
<td>Head of right caudate</td>
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<td>Generalised seizures</td>
<td>Right insular glioma involving right insula</td>
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<td>Head of right caudate</td>
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<tr>
<td>9</td>
<td>Partial seizures</td>
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<td>No worsening</td>
<td>Head of right caudate</td>
<td>Anarthria induced by stimulation of head of right caudate</td>
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<tr>
<td>10</td>
<td>Generalised seizures</td>
<td>Left insular glioma involving left insula</td>
<td>Mild dysarthria</td>
<td>Head of left caudate</td>
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<td>Recovery; return to normal life</td>
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</tr>
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<td>11</td>
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#### Clinical results

There was no postoperative sensorimotor deficit. However, nine patients had transient slight to moderate language worsening postoperatively:

- three patients (Nos 2, 3, and 4) operated on for a left insula glioma experienced transitory dysarthria;
- five patients (Nos 6, 7, 8, 9, and 11) operated on for a glioma invading the dominant fronto-mesial structures had slowness of speech corresponding to a transitory “dominant supplementary motor area syndrome,” as previously described,44 with perseveration;
- one patient (No 10), with a more anterior fronto-mesial glioma (in front of the supplementary motor area), experienced transient perseveration.

All symptoms disappeared within 10 days to three months.

One patient (No 1) with a left insular tumour had no postoperative language worsening, while the patient (No 5) who experienced mild preoperative dysarthria improved immediately after surgery.

#### Radiological results

In all cases, postoperative MRI showed that the cavity came into the contact with the striatum. In the five insular lesions, the resection was stopped at the level of the lateral part of the left putamen (fig 1C). Owing to tumour infiltration in the subcortical areas in four patients, the resections were total in one case and subtotal in four.

In the six fronto-mesial precentral lesions, lesion removal was interrupted at the level of the head of the caudate nucleus—on the left side in four cases (fig 2C) and on the right side in two. The resections were total in three patients and subtotal in three.

The results of the histopathological examination revealed a low grade glioma (World Health Organisation grade II) in all cases. No patient had chemotherapy or radiotherapy.

#### DISCUSSION

In this study we used the technique of intraoperative direct electrical stimulation in conscious patients. This is known to represent a safe, accurate, reliable, and reproducible method of real time identification of the cortical and subcortical (white matter and grey nuclei) structures essential for language function during surgical resection of tumours.16 Electrical mapping has been shown to be a valuable adjunct in decreasing postoperative morbidity while improving the quality of resection, especially in brain tumour surgery, producing better outcomes than surgery without mapping.17,18 This technique also allows analysis of the type of language disturbance induced by each stimulation, and then correlation of the clinical symptoms with the location
of the site stimulated. This anatomo-functional study can help determine different eloquent subregions within a wider area, here the dominant striatum. In practice, macroscopic identification of the putamen or the caudate was anatomically very clear in all cases, as these structures are easily distinguishable from the white matter. However, the motive for using subcortical stimulation was to identify specific striatal functions, particularly for language, in order to avoid permanent postoperative deficits. Finally, although all our patients had structural lesions, language disorders only occurred when stimulating at specific electrode positions. In addition, motor responses to cortical stimulation had a distribution (hand/finger—superior, face/mouth—inferior) appropriate for the primary motor cortex. These findings suggest that our observations accurately reflected the functional anatomy of the regions tested, as we previously reported in other brain areas involved by low grade gliomas.36 38

To our knowledge, few data are currently available on striatal mapping, owing to the fact that gliomas involving this structure are rare and generally not operated on except in the non-dominant hemisphere.45 Furthermore, although chronic stimulation of the basal ganglia (left or right) is often used in the treatment of movement disorders, the electrode is generally implanted within the subthalamic nucleus, the pallidum, or the thalamus—allowing improved understanding of the pathophysiology of these structures, in particular for language—but only exceptionally in the striatum. Striatal stimulation has been used for epilepsy treatment, but little attention has been paid to striatal mapping.47

Our results are strongly in favour of a key role of the dominant striatum in language, anatomically clearly identified in all 11 patients. Indeed, in all the patients, stimulation of this structure systematically elicited language disturbances which led to termination of tumour removal. Moreover, the functions attributed to the putamen and caudate seem to be language specific, as there were no facial or limb motor effects during stimulation. Control MRI showed that all resections came into contact with the striatum, thus confirming that the language disorders described intraoperatively were definitely caused by stimulation of the putamen and caudate nucleus and not by stimulation of the language fibres. The latter induces different symptoms from those elicited during striatal mapping, as we have shown previously using the same methodology.46 Conversely, the fact that 10 of the 11 patients had transient postoperative worsening of language function while intraoperative testing was normal did not allow us to differentiate between dysphasia caused by resection near the cortical language sites (with the occurrence in five cases of a typical supplementary area syndrome), or near the white fibres, or near the striatum (because of transient post-surgical oedema). Interestingly, despite the rarity of this kind of study, Van Buren observed in 1963, during surgery for basal ganglia disorders, that lower range electrical stimulation at the level of the head of the caudate nucleus induced a “disturbance in which the impulse to speak has been dulled or forgotten”.

Another important result of this study is that the dominant striatum rather than the left striatum was shown to be implicated in language, as at the cortical level. Indeed,
in the depth of the cavity; at this level (star), subcortical stimulation language fibres (tag 43), eliciting anomia when stimulated. The resection posteriorly by the pyramidal pathways (tags 42 and 46) and laterally by repeated stimulation of the white matter; the boundaries were formed fronto-mesial structures, with functional boundaries detected using electrical stimulation, are marked by number tags as follows: 2, 1, anterior; P, posterior; M, midline). The eloquent cortical sites, identified using magnetic resonance imaging (MRI), showing a left fronto-mesial low grade glioma involving the superior part of the head of the caudate nucleus (arrow). Interestingly, cortical stimulation never seemed to be most implicated in the control of language, because dysarthria or anarthria is elicited when it is stimulated, and two patients experienced transient postoperative articulation disorders following insular glioma resection up to the left putamen. These results are in agreement with those provided by lesional and neurofunctional studies. Indeed, many investigators have reported speech planning disorders after infarction or haemorrhage involving the left putamen. Furthermore, positron emission tomography (PET) and fMRI data suggested a participation of the left putamen during repetitions of single words or single syllables, particularly at lower frequencies. Klein et al also found left putaminal activation when speaking a second language, and hypothesised that this region plays a special role for planning complex motor sequences of articulation. Thus it is conceivable that direct stimulation of the dominant putamen induces anarthria, supporting the view that this structure is widely involved in the motor act of speech, and that the processes immediately prior to the execution of articulation are strongly lateralised (though it is well known that the articulatory muscles receive innervation from both cerebral hemispheres). Indeed, we previously reported that resection of the non-dominant striatum did not elicit any postoperative aphasia or anarthria, although we previously reported that resection of the non-dominant striatum did not induce any permanent postoperative deficit, in particular no aphasia, in the left handed patients in the present series, electrical mapping identified right sided cortical sites within the premotor area that are involved in language (as in the left hemisphere in right handed patients). It also showed the implications of the right head of the caudate nucleus in language, as perseveration was elicited when it was stimulated, in the same was as stimulation of the left caudate nucleus in right handed patients. In addition, language pathways were also detected and followed from the cortex to the striatum.

These data thus argue in favour of the existence of right cortico-subcortical loops including the striatum (not only right cortical sites or right cortico-cortical networks), which are implicated in language in left handed patients. Such a result might lead to a better definition of the hemispheric “dominance” for language, which is still a matter of debate, based on individual data from cortical and subcortical striatal mapping. Nevertheless, as it is currently well known that there is no direct linear relation between handedness (evaluated here using the Oldfield questionnaire) and language dominance, another potential interpretation is that subcortical striatum bilaterally could be implicated in language function, at least in some left handers.

A third observation in this study is that the dominant striatum seems to be organised in at least two subregions, each playing a different role in language: the anterior putamen and the head of the caudate nucleus. The anterior putamen could be more specifically involved in the coordination of articulation, because dysarthria or anarthria is elicited when it is stimulated, and two patients experienced transient postoperative articulation disorders following insular glioma resection up to the left putamen. These results are in agreement with those provided by lesional and neurofunctional imaging studies. Indeed, many investigators have reported speech planning disorders after infarction or haemorrhage involving the left putamen. Furthermore, positron emission tomography (PET) and fMRI data suggested a participation of the left putamen during repetitions of single words or single syllables, particularly at lower frequencies. Klein et al also found left putaminal activation when speaking a second language, and hypothesised that this region plays a special role for planning complex motor sequences of articulation. Thus it is conceivable that direct stimulation of the dominant putamen induces anarthria, supporting the view that this structure is widely involved in the motor act of speech, and that the processes immediately prior to the execution of articulation are strongly lateralised (though it is well known that the articulatory muscles receive innervation from both cerebral hemispheres). Indeed, we previously reported that resection of the non-dominant striatum did not elicit any postoperative aphasia or anarthria, despite the fact that the patients were not awake in the preliminary study.

The supero-medial part of the head of the caudate nucleus seems to be most implicated in the control of language (selection/inhibition), as perseveration is elicited when it is stimulated. Moreover, six patients experienced transient perseveration (associated with a dominant supplementary motor area syndrome in five) following the resection of a glioma involving the fronto-mesial structures up to the caudate nucleus. Interestingly, cortical stimulation never elicited perseveration in these patients. Thus it is likely that induced perseveration, so the surgical procedure was stopped. (C) Postoperative coronal enhanced T1 weighted MRI, confirming that the resection was interrupted at the point of contact with the superior and medial part of the head of the left caudate (arrow).
this symptom was generated directly by a disturbance of caudate function (as an essential epicentre of the network), and not by spread of electrical stimulation. These results are also in accordance with those provided by lesional and neurofunctional imaging studies. Indeed, the role of lesions of the head of the left caudate nucleus in perseverative errors on a picture naming test has already been suggested.19,20 Levitt et al21 also reported significant inverse correlations between caudate nucleus volume and the severity of perseveration in working memory tasks in subjects with schizotypic personality disorder. This is consistent with the general function of the caudate in response selection and control.22 Moreover, using PET during the learning of a novel motor task that required inhibition of a previously learned motor sequence, Shadmehr and Holcomb23 showed that perseveration of a competing motor memory may be linked to reactivation of the neural circuit that participated in acquiring that memory—that is, the left putamen and the bilateral dorsolateral prefrontal cortex. Conversely, in subjects without perseveration, motor learning of a novel task again involved the striatum, but this time in the left caudate, which showed changes in regional cerebral blood flow during the reversal of the learning problem when the previously acquired motor memory was successfully gated. On the basis of this model, we can hypothesise that in our series, stimulation connected to the head of the dorsal cortex, which may inhibit the "inhibitory" role of this structure, thus resulting in reactivation of the neural circuit that participated in the naming of the previous picture (probably involving the putamen), explaining the occurrence of perseverance. Further studies are required to determine more accurately whether intraoperative stimulation elicits disturbance of a specific language network, or whether it interrupts a more general striato-prefrontal "cognitive" (supramodal) loop useful to language.

Conclusions
Our results are in agreement with the concept of two separate basal ganglia systems proposed by Middleton and Strick24: one mediated by the putamen (the "sensorimotor" part of the striatum, connected to the sensorimotor cortex), which may have a motor role in language, explaining why direct stimulation of this structure inhibits articulatory sequences and thus elicits anarthria; and the other mediated by the head of the caudate nucleus (the "associative" part of the striatum, connected to the prefrontal cortex), which may have a role in cognitive control, explaining why direct stimulation induces failure to inhibit previously learned responses and thus generates perseveration.

Such improved knowledge of the role of each subregion of the dominant striatum in language may have implications in surgical strategy in lesions involving this structure. Indeed, although we previously reported that resection of tumours invading the right non-dominant striatum was possible without inducing any permanent postoperative deficit,45 the present studies support the view that the dominant striatum should be preserved, because it still plays a key role in language even when invaded by a low grade glioma, though it is known to be capable of functional reorganisation.19 These observations, showing that functional tissue may persist within low grade gliomas at the level of the grey nuclei, complete the series which previously described the same phenomenon at the cortical level.10

The practical lesson for the neurosurgeon is that surgery should be undertaken with the patient awake and with electrical language mapping where tumours near to or within the dominant striatum are to be resected. The goal should be to interrupt lesion removal at the point of contact with the cortico-subcortical language loops—that is, at the functional boundaries represented by the cortical language sites—then at the corresponding language pathways, and then at the dominant putamen or caudate nucleus in the depth of the cavity. Complementary cognitive tasks may be considered in the future to further improve the quality of intraoperative striatal mapping.

The present data do not allow us to determine with certainty what would have happened if the language sites detected by stimulation within the dominant striatum had been resected to improve the quality of glioma removal. Indeed, we previously reported that brain areas considered as essential for language could sometimes be resected—in one or two surgical procedures—because of the functional reshaping mechanisms induced by the lesion or by the surgery itself.46 However, the frequent permanent aphasias reported after lesions of the dominant striatum demand caution before making any decision to resect this structure—even though its function could eventually be compensated by other brain areas, as already shown for the right striatum.43 Consequently, a multimodal study of this complex area is needed (combining the data obtained using intraoperative electrical mapping and those obtained by preoperative and postoperative functional neuroimaging), to improve our understanding of its integration in language networks, in particular its relation to the other structures involved in speech production, and to apply this knowledge to the surgery of striatal lesions. This work is currently in progress in our institution.

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