Awake mapping for low-grade gliomas involving the left sagittal stratum: anatomofunctional and surgical considerations

Clinical article

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Object. Preserving function while optimizing the extent of resection is the main goal in surgery for diffuse low-grade glioma (DLGG). This is particularly relevant for DLGG involving the sagittal stratum (SS), where damage can have severe consequences. Indeed, this structure is a major crossroad in which several important fascicles run. Thus, its complex functional anatomy is still poorly understood. Subcortical electrical stimulation during awake surgery provides a unique opportunity to investigate white matter pathways. This study reports the findings on anatomofunctional correlations evoked by stimulation during resection for gliomas involving the left SS. Surgical outcomes are also detailed.

Methods. The authors performed a review of patients who underwent awake surgery for histopathologically confirmed WHO Grade II glioma involving the left SS in the neurosurgery department between August 2008 and August 2012. Information regarding clinicoradiological features, surgical procedures, and outcomes was collected and analyzed. Intraoperative electrostimulation was used to map the eloquent structures within the SS.

Results. Eight consecutive patients were included in this study. There were 6 men and 2 women, whose mean age was 41.7 years (range 32–61 years). Diagnosis was made because of seizures in 7 cases and slight language disorders in 1 case. After cortical mapping, subcortical stimulation detected functional fibers running in the SS in all patients: semantic paraphasia was generated by stimulating the inferior frontooccipital fascicle in 8 cases; alexia was elicited by stimulating the inferior longitudinal fascicle in 3 cases; visual disorders were induced by stimulating the optic radiations in 5 cases. Moreover, in front of the SS, phonemic paraphasia was evoked by stimulating the temporal part of the arcuate fascicle in 5 patients. The resection was stopped according to these functional limits in the 8 patients. After a transient postsurgical worsening, all patients recovered to normal results on examination, except for the persistence of a right superior quadrantanopia in 5 cases, with no consequences for quality of life. The 8 patients returned to a normal social and professional life. Total or subtotal resection was achieved in all cases but one.

Conclusions. The authors suggest that the use of intrasurgical electrical mapping of the white matter pathways in awake patients opens the door to extensive resection of DLGG within the left SS while preserving the quality of life. Further anatomical, clinical, radiological, and electrophysiological studies are needed for a better understanding of the functional anatomy of this complex region.

Key Words • awake surgery • sagittal stratum • language mapping • visual mapping • subcortical electrostimulation • low-grade glioma • oncology

Abbreviations used in this paper: AF = arcuate fascicle; DLGG = diffuse low-grade glioma; DO = dénomination orale; IFOF = inferior frontooccipital fascicle; ILF = inferior longitudinal fascicle; KPS = Karnofsky Performance Scale; ORs = optic radiations; SS = sagittal stratum.
ment at a center that favored biopsy and watchful waiting (median survival 5.9 years, 95% CI 4.5–7.3 years). In addition, the French Glioma Network published the largest surgical series of DLGGs ever reported, in which it was shown with an experience of 1097 patients that extent of resection as well as postsurgical residual volume were independent prognostic factors significantly associated with a longer overall survival (according to multivariate analysis; median survival 13 years since the first treatment in the whole series).

Therefore, according to the current European Guidelines, “surgical resection represents the first therapeutic option in DLGGs.”

It is a major concern in surgery for DLGG that these mostly young patients, who usually present with no or only mild neurological deficits, retain their functional independence. Good functional outcome implies not only the absence of significant neurological worsening but ultimately a return to previous lifestyle and work after surgery. From this perspective, DLGG within the sagittal stratum (SS), especially in the left hemisphere, poses a surgical challenge because damage may result in severe language or visual deficits, with grave repercussions in patients’ quality of life.

The SS is a large, sheetlike, sagittal structure located lateral to the atrium of the lateral ventricle. Its boundary is arbitrarily defined at the axial level of the splenium of the corpus callosum. Its anterior limit is represented by the arcuate fascicle (AF). This region is a major crossroad, which includes several white matter tracts; that is, the inferior frontooccipital fascicle (IFOF), the optic radiations (ORs), and the inferior longitudinal fascicle (ILF). There is no agreement in the literature regarding the inclusion of the tapetum in the mesial SS. Beyond its anatomy, the actual role of the SS in brain functions remains poorly understood. In addition, there is to our knowledge no surgical series specifically dedicated to glioma resection within the SS. Interestingly, subcortical electrical stimulation during awake procedures provides a unique opportunity to study axonal connectivity.

Here we report for the first time a homogeneous series of 8 patients who underwent awake surgery for a DLGG involving the left SS. The goal was both to investigate the functional anatomy of this poorly studied region with the use of intraoperative electrical mapping and to apply this knowledge to the optimization of surgical outcomes.

Methods

Selection of Patients

From a prospective database we performed a review of patients who underwent awake surgery for histopathologically confirmed WHO Grade II glioma (DLGG) involving the left SS in our department between August 2008 and August 2012. Information regarding clinical characteristics (age at treatment, sex, neurological status); radiological features; surgical procedures (results of functional cortical and subcortical brain mapping); and outcomes was collected and analyzed.

Preoperative Evaluation Method

In addition to preoperative neurological examination, handedness was assessed using a standardized questionnaire (Edinburgh inventory). Furthermore, a speech therapist assessed language function by evaluating the level of fluidity and informativity of spontaneous speech. The DO (dénomination orale) 80 picture-naming task, which consists of 80 black-and-white pictures selected based on variables such as frequency, age of acquisition, and level of education, was administered to each patient. The preoperative language examination was performed 1 day before surgery. Finally, The Karnofsky Performance Scale (KPS) score was evaluated for each patient.

The topography of the tumor was accurately analyzed on a preoperative MRI study (T1-weighted and spoiled-gradient images obtained before and after Gd enhancement in the 3 orthogonal planes, T2-weighted axial images, and FLAIR-weighted axial images). Preoperative tumor volume was calculated based on T2- and FLAIR-weighted MRI signal abnormalities by 2 independent neurosurgeons (E.C.S. and H.D.). Tumor volume was assessed using dedicated software (Myrian, Intrasense).

Surgical Procedure

All surgical procedures were performed using an asleep-asleep technique with direct stimulation mapping, a method extensively described by the authors. A wide craniotomy exposing the sylvian fissure, the premotor cortex, and the temporoorbital junction was performed with the patient under sedation. The tumor margins were verified with ultrasonography in relation to the sulcal and gyral brain surface anatomy. Sterile letter tags marked the cortical boundaries of the glioma.

Prior to tumor resection, cortical mapping was performed in the awake condition to avoid damage to eloquent areas. A bipolar electrode (Nimbus, Newmedic) with 5-mm tip spacing was used to apply electrostimulation with a biphasic current intensity between 1.5 and 3 mA (60-Hz pulse frequency, 1-msec single-pulse phase, 4-second tissue contact) while the patient performed functional tasks. First, patients were asked to count from 1 to 10 over and over, with the goal of determining the optimal threshold of current intensity, from a baseline of 1.5 mA in cumulative steps of 0.5 mA until a reproducible response was obtained—that is, the intensity eliciting a complete speech arrest when stimulating the ventral premotor cortex. In this series, intensities between 1.5 and 3 mA were selected as the optimal stimulation threshold.

Then, intraoperative language mapping was performed using a picture-naming task (DO 80). Every picture was preceded by a short sentence for the patient to read (the French translation of “This is a….”). A speech therapist analyzed the following language disorders: speech arrest, anomia, articulatory troubles, phonemic paraphasia (disorder of the phonological form of the word), semantic paraphasia (disorders of the meaning of the word), speech slowness, initiation troubles, and perseveration. The patient and speech therapist were unaware of the timing of the application of electrostimulation. A cortical site was considered positive for language when any interference was met at 3 nonsequential stimulations, followed by normalization after stimulation. To avoid seizures the same site was never stimulated twice in succes-
Surgery for gliomas in the sagittal stratum

The duration of each stimulation was 4 seconds. The type of disturbance (sensorimotor, language, or visual deficit) was detailed by a speech therapist who was always present in the operating room during the functional mapping. Numbered sterile tags marked the eloquent areas. A photograph was taken before resection to capture the cortical map.

After completion of cortical mapping, tumor removal started. Subcortical stimulation was regularly alternated with resection, using the same electrical parameters as those at the cortical level. For the naming task, the same DO 80 picture task used during the cortical stimulation was applied. Given the brevity of each direct cortical stimulation, the surgical situation imposed the use of simple tests and evaluations based on short answers throughout the resection. The DO 80 images were presented in a continuous loop on a computer screen placed in front of the patient. The type of language disturbance (if present) was asked to inform us immediately when he/she perceived any abnormal sensation (hypesthesia, paresthesias, and so on), and to describe it. If the same motor, somatosensory, and/or language response was obtained during at least 3 subcortical stimulations, the stimulated zone was marked with a sterile tag, as was done at the cortical level. In all cases, glioma removal was interrupted at this site, and the same procedure was performed again in the neighboring structures.

To perform optimal tumor resection, the procedure did not stop until eloquent pathways were found, which means that there was no margin left between the surgical cavity and the adjacent functional areas. Subcortically, in addition to the DO 80, a reading test was also taken by the patient. Furthermore, online mapping of the ORs was also achieved, to prevent hemianopia. To this end, a modified picture-naming task was used, with presentation of 2 objects situated diagonally on a screen divided into 4 quadrants. An image was presented in the quadrant to be saved and another image was presented in the opposite quadrant. Direct subcortical electrostimulation was repeatedly performed without the patient’s knowledge, until ORs were identified by eliciting transient visual disturbances such as blurred vision, shadow, phosphenes, or even visual illusions. Finally, a nonverbal semantic association test (the so-called pyramid and palm trees test [PPTT]) was administered. This task involves 52 black-and-white drawings presented on a computer screen. For each target picture, 2 new pictures are proposed, and the patient is asked to match one of these with the target one according to a semantic link, by pointing to the matching picture.

At the end of the resection, a photograph of the surgical cavity was taken to capture with the subcortical map.

Postoperative Course

Immediate postoperative assessment was achieved 3–5 days after surgery by using the same tests as performed preoperatively, and postoperative assessment was conducted 3 months after surgery. The KPS score was also evaluated 3 months after surgery.

Postoperative MRI (T1-, T2-, and FLAIR-weighted imaging) was performed within 24 hours after surgery to assess the extent of resection, at 3 months, and then every 6 months thereafter. Complete removal of the hyperintense area on postoperative FLAIR-weighted MRI sequences was considered to be total resection, whereas a residual volume of ≤ 10 ml on FLAIR imaging was defined as subtotal resection. All other cases were considered to be a partial resection.

In addition, we analyzed accurately the anatomical location of eloquent sites, by definition at the periphery of the surgical cavity, where the resection was stopped according to the functional responses elicited by intraoperative stimulation (with no margin). It is worth noting that we have extensively used this reliable and reproducible method in many previous studies.

Results

Clinicoradiological features, surgical management, and outcome in the 8 patients are summarized in Table 1.

Patient Population

Eight consecutive patients (6 men and 2 women) with a glioma involving the left SS underwent awake surgery in our department between August 2008 and August 2012. Of note, 1 patient (Case 3) has already been described in a previous report. The patients’ mean age was 41.7 years (range 32–61 years). Seven patients were right-handed, and 1 was ambidextrous. Seven patients presented with seizures as first symptoms (4 patients with intractable epilepsy), whereas 1 patient experienced missing words. Results of the neurological examination were normal in 2 cases. Six patients had slight language disturbances (slowness of verbal fluency or naming disorders during DO 80). The KPS score was 90 in all cases.

Preoperative MRI studies showed a tumor involving the left SS in all cases; that is, within the temporooccipital junction around the atrium. The mean preoperative tumor volume was 64.4 ml (range 10–180 ml) (Fig. 1A).

Intraoperative Brain Mapping

Mapping identified eloquent language areas in all patients, indicating crucial participation of the left hemisphere in language in the 8 cases (also for the ambidextrous patient).

At the cortical level, stimulation of the ventral premotor cortex (lateral part of the precentral gyrus) induced a speech arrest in the 8 patients; that is, the loss of the motor ability to speak (no sound, no movement of the
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Presenting Sxs</th>
<th>Neuro Exam, KPS Score</th>
<th>Preop Tumor Vol (ml)</th>
<th>Intraop Findings</th>
<th>Postop Findings</th>
<th>EOR, Residual Vol (ml)</th>
<th>Last KPS Score</th>
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<td>seizure</td>
<td>normal, 90</td>
<td>10</td>
<td>cortex: SA (vPMC), anomia (pst STG, pst MTG), alexia (pst ITG &amp; basal TOJ) WM: sem (IFOF), vis dis (ORs), alexia (ILF)</td>
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<td>normal except RSQ</td>
<td>STR, 6</td>
<td>90</td>
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</table>

* comp = comprehension; dis = disorders; EOR = extent of resection; FU = follow-up; ITG = inferior temporal gyrus; lang = language; mid = middle; MTG = middle temporal gyrus; neuro exam = neurological examination; phon = phonemic paraphasia; PR = partial resection; pst = posterior; RSQ = right superior quadrantanopia; SA = speech arrest; sem = semantic paraphasia; SMG = supramarginal gyrus; STG = superior temporal gyrus; STR = subtotal resection; Sxs = symptoms; TOJ = temporooccipital junction; TR = total resection; vis = visual; vPMC = ventral premotor cortex; WM = white matter.
Anomia was elicited in all patients, by stimulating the temporal cortex in 7 of them (posterior part of the superior temporal gyrus in 4 cases and midpart of the superior temporal gyrus in 1 case, posterior part of the middle temporal gyrus in 2 cases, posterior part of the inferior temporal gyrus in 1 case) and by stimulating the inferior part of the supramarginal gyrus in 1 patient. In addition, phonemic paraphasia was generated in 2 cases during stimulation of the midpart of the superior temporal gyrus, and semantic paraphasia was elicited in 3 cases during stimulation of the posterior part of the superior temporal gyrus (2 cases) or posterior part of the middle temporal gyrus (1 case). Finally, alexia was induced by stimulating the posterior part of the inferior temporal gyrus and the basal temporoooccipital junction in 1 patient.

At the subcortical level, axonal mapping detected functional fibers in all patients: semantic paraphasia was generated by the stimulation of the upper part of the cavity in all cases, corresponding to the IFOF; alexia was elicited during the stimulation of the basal part of the cavity in 3 cases, corresponding to the ILF; in between, in the depth of the cavity, visual disorders were induced by stimulating the ORs in 5 cases; and phonemic paraphasia was evoked by stimulating the anterior part of the cavity. -
ity in 5 patients, corresponding to the temporal part of the AF (Fig. 1B). The resection was stopped according to these functional limits in the 8 patients.

**Postoperative Course**

In the immediate postoperative period all patients developed a transient language deficit; that is, comprehension disorders in 2 cases, naming disorders in 2 cases, and reading deficit in 5 cases. Five patients also experienced deficit in visual field (right superior quadrantanopia). All patients benefited from specific language rehabilitation within the weeks following surgery. Three months after surgery, the 8 patients had recovered to normal results on examination, except for persistence of a right superior quadrantanopia in 5 cases, with no consequences for the quality of life. All patients had a normal DO 80 score (that is, between 78 and 80). They returned to a normal social and professional life in all cases, including driving.

On postoperative MRI, according to Berger’s classification,1 1 patient had a total resection (no residual abnormality), 6 had a subtotal resection (residual high signal on FLAIR-weighted MRI ≤ 10 ml), and 1 had a partial resection (residual high signal on FLAIR > 10 ml). The mean postoperative volume of residual tumor was 5.8 ml (range 0–20 ml) (Fig. 1C and Fig. 2).

The neuropathological examination revealed a WHO Grade II glioma in 8 cases. No patient had adjuvant treatment after resection. The mean follow-up period after surgery was 32 months (range 12–48 months). At the most recent follow-up visit, all patients had a KPS score of 90 or 100.

**Discussion**

Although DLGGs are frequently located within the supplementary motor area or the insular lobe, they rarely involve the posterior regions of the brain.11,47 For example, it has recently been reported that occipital DLGGs represented only 2% of the whole population of DLGG patients.52 In this setting, DLGG of the SS is a rare entity, raising specific surgical issues due to the high density of white matter tracts running in this region. To our knowledge, this is the first series dedicated to the surgical anatomy and postoperative outcomes in DLGGs involving the left SS.

**Anatomical Considerations**

Even though it is well agreed that ORs run within the SS, the anatomy of this brain structure remains poorly understood.31 For example, the inclusion of the ta
tetum38 or middle longitudinal fascicle in SS22,41 is still under debate. According to Mori et al.,42 “This structure seems contiguous to the posterior region of the corona radiata, its main constituent being the optic radiations. It also contains association fibers, most notably the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus.” Recent advances in diffusion tensor imaging tractography in vivo as well as a return to fiber dissection in cadavers have allowed a better anatomical knowledge of this complex area.3,38,44 These data showed that the ILF, which connects the occipital lobe with the anterior part of the temporal lobe, runs within the SS, laterally and inferiorly to the lateral wall of the temporal horn. It is located just laterally and under the ORs, which emerge from the lateral geniculate body and run around the roof of the occipital horn to terminate into the calcarine sulcus. The IFOF runs on the lateral and superior wall of the ventricle. Coming from the frontal lobe, the IFOF crosses the anterior portion of the temporal isthmus; it passes above the anterior portion of the roof of the temporal horn; it turns superiorly, passing underneath the posterior insula; and then it joins the SS in the superior portion of the lateral surface of the atrium, superficially to the ORs and above the ILF, to reach the parietal and occipital lobes as well as the basal temporoooccipital junction.25 Therefore, because SS is a neural crossroad, surgery within this area has a high risk of generating multiple disconnections, and of inducing permanent neurological deficits.

**Surgical and Functional Considerations**

The goal of surgery for DLGG is to optimize the onco-functional balance; that is, to increase the extent of resection while preserving brain functions.18,21 To this end, functional mapping for guided resection performed using intraoperative direct stimulation was extensively demonstrated as representing a reliable and efficient technique to maximize the benefit/risk ratio of DLGG in eloquent areas.4,6,9,24 Intrasurgical electrical mapping is particularly useful to identify the white matter tracts, because the brain’s plastic potential is low at the subcortical level: any damage of the neural continuity will generate permanent deficits.2,28

In this study we used intraoperative axonal electrostimulation in awake patients to map the different pathways running in the SS. Thanks to this method, original anatomofunctional correlations have been performed, enabling a better understanding of the role of this cerebrum. Indeed, although the cortical electrical mapping before tumor removal allowed the detection of at least 1 site eliciting anomia, paraphasia, or alexia in the midpart or posterior part of the superior, middle, or temporal gyrus in all patients (that is, in front of or above the SS), there were nonetheless no eloquent sites found by stimulating the cortex over the SS. As a consequence, this cortex invaded by the DLGG was resected in the 8 patients, giving access to the SS. Interestingly, despite the lack of cortical response, it was possible to induce distinct neurological disorders by stimulating specific parts of the surgical cavity; namely, semantic paraphasia, alexia, and visual disturbances during stimulation of the upper, basal, and deep part of the cavity, respectively. These results mean that 3 main fasciculi have been detected in the SS.

The first tract is the IFOF, which was identified in the 8 cases. Previous studies have demonstrated that the IFOF was involved in verbal and nonverbal language processing and that it subserved the ventral semantic stream.17,45 Indeed, its stimulation induced transient semantic paraphasia with a high level of reproducibility.15,19 In our series this symptom was elicited when stimulating the upper part of the surgical cavity; that is, the superior part of SS, where the IFOF is running according to the anatomical data described above. Therefore, it means that...
Surgery for gliomas in the sagittal stratum

the IFOF is a major functional landmark, which should lead the surgeon to stop the resection in the depth of the cavity when removing glioma within the SS.

The second fascicle is the ILF, which was detected in 3 cases. This pathway connects the occipital lobe with the basal posterotemporal cortex, which includes the visual word form area² and the visual object form area. The ILF is involved in reading and visual recognition.²⁰,²³ Indeed, Gaillard et al. described a patient in whom a specific and permanent reading deficit presented after surgery within the left visual word form area and the underlying white matter. With the use of postoperative tractography, they suggested that this alexia was due to injury of the left ILF. In the same vein, Mandonnet et al. elicited a transient deficit of visual recognition of objects during direct electrostimulation of the left ILF running within the SS. Here, reading disorders were generated when stimulating the deep and basal part of the surgical cavity; that is, the inferior part of the SS, where the ILF is running according to the anatomical data already mentioned. These findings are in agreement with a recent observation of double dissociation between visual recognition disorders and picture-naming disorders generated during stimulation of left ILF and IFOF, respectively.²³ Thus, ILF also represents a crucial functional boundary at the end of tumor removal in SS.

The third tract is the ORs, which were identified in 5 patients. Indeed, our team has recently developed a modified picture-naming task to detect visual pathways, with presentation of 2 objects situated diagonally on a screen divided into 4 quadrants. An image is presented in the quadrant to be saved; that is, in the right inferior quadrant, and another image is presented in the opposite (left superior) quadrant—to serve as a control. Using this protocol, transient visual disturbances have been evoked during stimulation of the depth of the surgical cavity; that is, the deep part of SS, where ORs are running according to the anatomical data. Visual pathways have been totally preserved in 3 cases and partially preserved in 5 cases with a right superior quadrantanopia, but no hemianopia has been generated. We have already reported that this partial visual deficit was well tolerated by patients because they can continue to enjoy a normal social and professional quality of life, including driving (no driver-license suspension if hemianopia is avoided).²⁵

Interestingly, even though this is not a component of the SS, the AF has been identified in 5 patients by eliciting phonemic paraphasia during stimulation of the anterior part of the surgical cavity. Indeed, it was previously shown that the AF, which connects the middle and inferior temporal gyri with the precentral gyrus and posterior portion of the inferior and middle frontal gyri, subserved phonological processing—thus generating phonemic disturbances when stimulated.¹⁴,¹⁹,³³ This fascicle represents the anterior limit of resection for glioma within the SS.

Understanding the complex functional anatomy of this area is crucial to resection of DLGGs involving the left SS, especially because these tumors often migrate along the main white matter tracts.³⁴ Indeed, the onset of transient postoperative neurological worsening in the 8 patients supports the fact that we were actually in contact with the functional pathways at the end of surgery, to optimize the extent of resection. In particular, in the 5 patients in whom ORs were detected in the depth, a right superior quadrantanopia (but no hemianopia) occurred postoperatively. In the same vein, postsurgical transitory reading disturbances have been described only if ILF and/or ORs have been identified at the end of resection. It is nonetheless worth noting that thanks to intraoperative mapping, which enables practitioners to perform online structural-functional correlations throughout the glioma removal, the quality of

Fig. 2. Cases 1–6 and 8. Preoperative axial FLAIR-weighted MRI (left panels), intraoperative photograph after tumor resection according to functional boundaries both at cortical and subcortical levels—eloquent structures are marked by number tags (middle panels), and postoperative axial FLAIR-weighted MRI (right panels).
life was preserved in the 8 patients while achieving a total or subtotal resection in all but 1 case.

Conclusions
Diffuse low-grade glioma rarely involve the SS. In this series, we observed that the left SS was a neural crossroad composed of ILF, ORs, and IFOF, behind the temporal part of the AF. Thus, glioma resection in this brain area may induce multiple subcortical disconnections, which could generate major irrevocable deficits; that is, reading, visual, and naming disorders. We suggest that the use of intrasurgical electrical mapping of the white matter pathways in awake patients may open the door to extensive resection of DLGG within the left SS while minimizing neurological morbidity. Further anatomical, clinical, radiological, and electrophysiological studies are needed for a better understanding of the functional anatomy of this complex region.

Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Duffau. Acquisition of data: all authors. Analysis and interpretation of data: Duffau, Chan-Seng. Drafting the article: Duffau, Chan-Seng. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Duffau. Administrative/technical/material support: Duffau. Study supervision: Duffau.

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Surgery for gliomas in the sagittal stratum

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