

Motor imagery in normal subjects and in asymmetrical Parkinson's disease

A PET study

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Article abstract—*Objective:* To investigate, using PET and $H_2^{15}O$, brain activation abnormalities of patients with PD during motor imagery. To determine whether motor imagery activation patterns depend on the hand used to complete the task. *Background:* Previous work in PD has shown that bradykinesia is associated with slowness of motor imagery. *Methods:* The PET study was performed in eight patients with PD with predominantly right-sided akinesia, and in eight age-matched control subjects, all right-handed. Regional cerebral blood flow was measured by PET and $H_2^{15}O$ while subjects imagined a predetermined unimanual externally cued sequential movement with a joystick with either the left or the right hand, and during a rest condition. *Results:* In normal subjects, the prefrontal cortex, supplementary motor area (SMA), superior parietal lobe, inferior frontal gyrus, and cerebellum were activated during motor imagery with either the left or the right hand. Contralateral primary motor cortex activation was noted only when the task was imagined with the right (dominant) hand, whereas activation of the dorsolateral prefrontal cortex was observed only during imagery with the left hand. In patients with PD, motor imagery with the right (“akinetic”) hand was characterized by lack of activation of the contralateral primary sensorimotor cortex and the cerebellum, persistent activation of the SMA, and bilateral activation of the superior parietal cortex. Motor imagery with the left (“non-akinetic”) hand was also abnormal, with lack of activation of the SMA compared with controls. *Conclusions:* In patients with PD with predominantly right-sided akinesia, brain activation during motor imagery is abnormal and may appear even with the less affected hand. In normal subjects, brain activation during motor imagery depends on the hand used in the imagined movement.

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PD is characterized clinically by the association of akinesia, rigidity, and resting tremor related to a dopaminergic deficiency of the nigrostriatal pathway. Several electrophysiologic studies have demonstrated that motor preparation is affected in PD.^{1,2} Another approach to studying motor processing relies on the motor imagery paradigm, which consists of the internal rehearsal of a given movement without overt motor output. In normal subjects, different studies suggest that motor execution and motor imagery share common motor circuits.^{3–5} It has also been demonstrated that asymmetries arising from motor dominance in real movements also occur for imagined movements.⁶ We have recently shown in a chronometric study in right-sided hemiparkinsonian patients that motor execution asymmetry favoring the left hand was also associated with motor imagery asymmetry.⁷ Patients mentally simulated movement more slowly with their right (affected) hand than with their left hand.

Neuroimaging techniques such as PET or SPECT may provide a better understanding of the physiologic basis of motor imagery by measuring changes

in regional cerebral blood flow (rCBF). In normal subjects, most of the motor, premotor, prefrontal, and parietal regions activated during motor execution are also activated during motor imagery.^{8–17} Several PET and SPECT studies have focused on motor execution in PD.^{18–27} Conversely, no systematic investigation of brain activation during motor imagery has been performed, to our knowledge, in patients with PD.

The current study was designed to measure rCBF changes using PET and $H_2^{15}O$ during mental imagery of a unimanual motor task in patients with PD and in right-handed control subjects. Our objectives were twofold: 1) To determine the brain activation abnormalities underlying the impaired motor imagery in patients with PD. 2) To assess whether motor imagery activation patterns depend on the hand, akinetic or not, dominant or not, used to complete the task. For these purposes, we studied a group of right-handed patients with PD with mild to moderate akinesia affecting essentially the right hemibody and sparing the left one, as well as a group of right-handed normal subjects.

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Table 1 Clinical data of eight patients with PD

Patient no./sex/age, y	Disease duration, y	UPDRS off-drug motor score	Tapping test, % of asymmetry	Hoehn and Yahr score	L-dopa daily dose, mg
1/F/49	2	21	31.7	2	700
2/M/47	9	36	10	3	200
3/M/50	7	11	24	1.5	300
4/M/54	4	20	13.6	1.5	300
5/F/58	3	12	18.9	1.5	0
6/F/37	1	8	16.2	1	0
7/M/38	9	23	10	2.5	600
8/M/52	4	19	16	2	600
mean \pm SD: 49.4 \pm 5.3	4.9 \pm 2.6	18.7 \pm 6	17.5 \pm 16	2 \pm 0.5	540 \pm 217

UPDRS = Unified Parkinson's Disease Rating Scale.

Materials and methods. *Subjects.* We studied eight right-handed patients with PD (mean age 49.4 \pm 5.3 years, range 37 to 59; five men, three women). Inclusion criteria were the following: 1) idiopathic PD according to the criteria of the United Kingdom Parkinson's Disease Brain Bank²⁸; 2) positive and sustained response to dopaminergic treatment at the time of the study or confirmed at follow-up; 3) clear asymmetric parkinsonian syndrome affecting predominantly the right hemibody; and 4) prominent akinetic-rigid signs without tremor. The clinical data for patients are presented in table 1. Six patients received a dopaminergic treatment, and two were drug-naïve with further follow-up demonstrating levodopa responsiveness. Assessment of disease severity and motor signs used the Hoehn and Yahr scale and Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) while patients were off-drug for at least 6 hours.²⁹ The degree of asymmetry of motor signs between each hemibody was defined by the hand tapping test score,³⁰ with at least a 10% right-left difference (mean difference was actually 17.5% \pm 15.9%), and a right-left difference of 2 points on item 25 (scoring 0 to 4) of UPDRS Part III.²⁹ Based on this clear asymmetry of signs and for purposes of simplification, the right hand of the patients with PD will be also called the "akinetic" hand and the left hand the "nonakinetic" hand. Eight age-matched, right-handed healthy control subjects who did not present any neurologic disease were studied (mean age 54 \pm 12.8 years; three men, five women). The handedness of the parkinsonian patients and of the normal subjects was assessed using the Annett Handedness Inventory.³¹ All patients and control subjects were familiarized and trained on motor imagery tasks by using a questionnaire and exercises given a few weeks before the PET scan.³² All treated patients were off-drug at the time of the PET study, with the last dose of antiparkinsonian treatment taken at least 6 hours before the scan acquisition.

This study was performed after approval by the Lyon University Hospitals Ethical Committee. All subjects participated after the nature of the procedure had been fully explained, and they signed an informed consent form according to the Declaration of Helsinki.

Activation tasks. Subjects were scanned while actually imagining a predefined sequential motor task. Subjects lay down on the bed of the PET scanner with their eyes closed. Three conditions were used, according to instructions

given to the subjects, as follows: imagination of the task with the right hand (IR), imagination of the task with the left hand (IL), and rest condition (RC). Before scanning, and after general instructions had been given, a few practice trials for each condition were performed to ensure that the task was properly understood. The motor task comprised a sequential movement performed with a joystick with the right or the left hand. Each of the motor conditions was repeated once in counterbalanced order, one in clockwise and one in counterclockwise order. Clockwise order consisted of moving the joystick to the right with a return to the center, then backward with a return to the center, and then to the left with a return to the center. After completion of this sequential imagined movement, subjects pressed with the index finger a button on the joystick that produced a low-tone auditory stimulus. After a random delay of 2,000 \pm 500 milliseconds, a higher-tone stimulus indicated to the subject to start the task again. This externally cued motor task was repeated in the same manner during 90 seconds for each condition, as quickly and accurately as possible. To control for the subject's motor imagery ability, completion times during actual execution and during motor imagery of the task were recorded. This was to verify that motor imagery completion time correlated with motor execution completion time. In addition, subjects were asked whether the task was easy to imagine or not. According to these two methods of controlling for the quality of motor imagery, one out of the nine originally selected patients was withdrawn from the study because of an abnormally short motor imagery completion time, reflecting great difficulties in imagining the task. No control subject was excluded from the study according to these criteria. The baseline (rest) condition, which was repeated once, was designed to replicate the finger movement (button press) and auditory stimuli present in all imagery trials and to avoid as much as possible involuntary motor imagery. The subject listened to a high-tone auditory stimulus. A variable period later (range 0.5 to 5.5 sec), a second lower-tone stimulus was produced that indicated to the subject to press the button situated on the joystick. This task was repeated during 90 seconds, as for the other conditions. This minimal motor task was common to all the conditions.

Scanning procedure. The head of the subject was maintained in a fixed position by using a thermoformed

mask. Control of the head position throughout the examination was made by laser alignment along with reference points on the Reid's line before and after each session. The PET tomograph was a Siemens CTI HR+ (Erlangen, Germany). Transmission data were acquired using rotating sources filled with $^{68}\text{Ge}/^{68}\text{Ga}$. Images were reconstructed by three-dimensionally filtered back projection (Hanning filter; cut-off frequency 0.5 cycles/pixel), giving a transaxial resolution of 6.5 mm full width at half maximum, and displayed in a 128×128 -pixel format with 63 planes creating approximately 2-mm cubic voxels. The rCBF was estimated by recording the distribution of radioactivity after an IV injection of 10 mCi of H_2^{15}O through a forearm cannula placed into the brachial vein. The integrated counts were collected for 90 seconds, starting 20 seconds after the injection. For data analysis we considered only the 60 seconds corresponding to the maximum radioactivity. A 10-minute interval was necessary between each test condition for adequate radioactivity decay.

PET image and statistical analysis. Image analysis was performed in MATLAB 4.2 (Math Works, Natick, MA) using software for statistical parametric mapping (SPM 96, MRC Cyclotron Unit, London, UK).³³ Individual PET scans were oriented along the intercommissural line using an averaged image from each subject and then transformed (normalized) into a standard stereotactic space.³⁴ Global differences in cerebral blood flow were covaried out for all voxels, and comparisons across conditions were made using *t* statistics with appropriate linear contrasts and then converted to *z* scores. Only regional activation significant at $p < 0.05$, uncorrected for multiple comparisons ($z > 3.10$), was considered. Activated foci above a *z* threshold of 4.25 correspond to a corrected $p < 0.05$ for multiple comparisons. Comparisons were made within each group, assessing the main effect of imagined movement versus rest for each hand (IL or IR – RC).

Results. Task performance in patients with PD. To evaluate the level of asymmetry of motor imagery and execution in the patients with PD, we compared their motor imagery completion times obtained during the scans with motor sequence execution times for sequences executed between scans. We performed a repeated-measures analysis of variance (ANOVA) in which the dependent variable was the sequence completion time and the within-subject variables were hand (left, right) and condition (imagery, execution). The mean completion time was shorter for the left hand than for the right hand ($5,177 \pm 1,532$ milliseconds versus $5,904 \pm 1,739$ milliseconds; ($F[1,7] = 7.8, p < 0.05$). Neither the effect for condition ($F[1,7] = 0.05$) nor the hand \times condition interaction ($F[1,7] = 0.5$) was significant. This indicates that the asymmetry holds for both execution and imagery. A separate repeated-measures ANOVA for imagery completion times confirmed that the completion time for imagined sequences was faster for the left hand ($5,245 \pm 1,840$ ms) than for the right ($5,882 \pm 1,863$ ms) ($F[1,7] = 7.9, p < 0.05$), and likewise the execution completion time for executed motor sequences was faster for the left hand ($5,109 \pm 1,278$ ms) than for the right ($5,925 \pm 1,734$ ms) ($F[1,7] = 5.9, p < 0.05$).

rCBF: Within-group comparisons in control subjects. **Main effect of motor imagery with the left hand.** When motor imagery with the left hand was compared with rest,

Table 2 Sites of activation in controls during motor imagery (*z* score > 3.10)

Activated areas	L/R	<i>z</i> Score	Stereotactic coordinates		
			x	y	z
Left hand					
SMA (BA 6)	L	3.73	-10	4	60
	R	3.45	10	-18	58
Lateral premotor cortex (BA 6)	L	3.5	-26	2	62
DLPFC (BA 9)	L	3.7	-50	2	42
Inferior frontal gyrus	L	3.75	-56	42	6
Superior parietal lobe (BA 7)	R	5.20	18	-78	56
	L	4.85	-22	-72	52
Cerebellar hemisphere	R	4.06	52	-54	-40
Right hand					
Primary motor cortex (BA 4)	L	3.43	-42	-18	60
SMA (BA 6)	L	3.68	-8	-8	68
Lateral premotor cortex (BA 6)	L	5.02	-30	-2	60
Superior parietal lobe (BA 7)	L	4.99	-22	-72	52
Cerebellar hemisphere	R	3.8	24	-50	-44

SMA = supplementary motor area; BA = Brodmann's area; DLPFC = dorsolateral prefrontal cortex.

significant activations were detected bilaterally in the superior parietal lobe (Brodmann area [BA] 7) and supplementary motor area (SMA); in the left lateral premotor cortex, inferior frontal gyrus (BA 46), and dorsolateral prefrontal cortex (DLPFC; BA 9 and 10); and in the right cerebellar hemisphere. No significant rCBF increase was observed in the primary motor cortex (table 2 and figure 1, A and B).

Main effect of motor imagery with the right hand. The activation pattern was different from the preceding. Indeed, when motor imagery with the right hand was compared with rest, significant activations were noted in the left primary motor cortex, lateral premotor cortex, SMA, DLPFC, and superior parietal lobe (BA 7) and in the right cerebellar hemisphere. No activation was found in the anterior cingulate cortex or in the prefrontal cortex (see table 2 and figure 2, A and B).

rCBF: within-group comparisons in patients with PD. **Main effect of motor imagery with the left hand.** When motor imagery with the left (nonakineti) hand was compared with rest, significant activations were seen bilaterally in the superior parietal lobe (BA 7), in the left anterior cingulate cortex, in the left lateral premotor cortex, in the left inferior frontal gyrus (BA 45), in the left DLPFC (BA 10), and in the occipital cortex (table 3 and figure 1, A and B).

Main effect of motor imagery with the right hand. When motor imagery with the right (akineti) hand was compared with rest, significant activations were noted in the left lateral premotor cortex and SMA, bilaterally in the superior parietal lobe (BA 7), in the DLPFC (BA 10), and in the right primary motor cortex (see table 3 and figure 2, A and B).

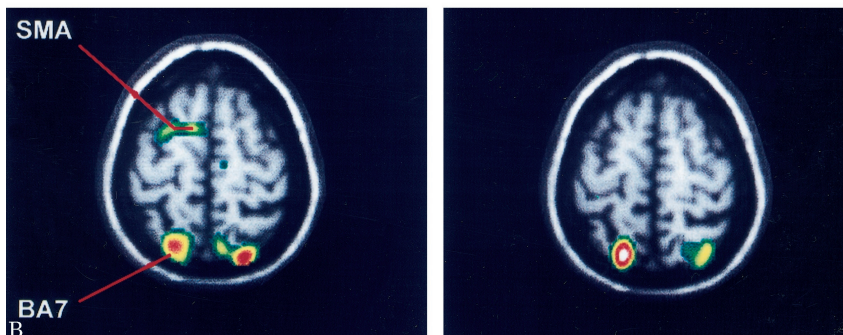
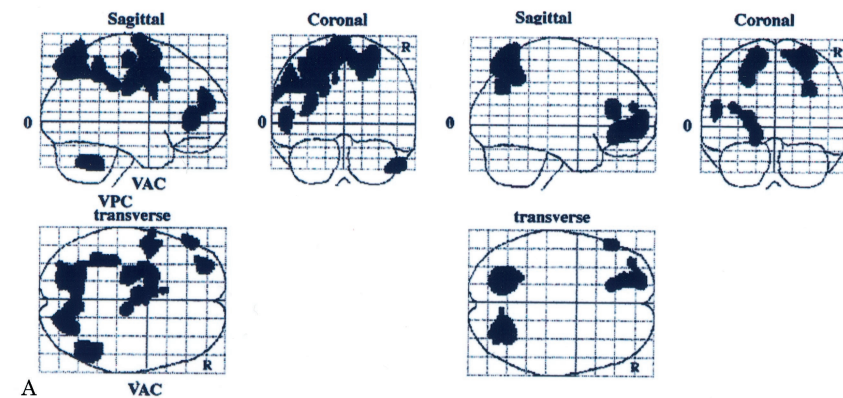


Figure 1. Motor imagery with the left hand versus rest condition. (A) Statistical parametric maps (SPM) of increased regional cerebral blood flow (rCBF) from the subtraction analysis (within-group study), showing the significantly activated areas for the control subjects (left panels) and the patients with PD (right panels). The SPM are displayed in the anatomic space of Talairach and Tournoux³⁴ as a maximum intensity projection viewed from the right side (sagittal view), the back (coronal view), and the top (transverse view) of the brain. (B) In the control group, increased rCBF (superimposed on an MR image of the brain) is seen in the left anterior supplementary motor area (SMA) and in the left and right superior parietal lobe (BA 7). In patients with PD, bilateral activation is seen in the superior parietal lobe, whereas no significant rCBF increase appears in the SMA. Activated regions are displayed in green, yellow, red, and white colors from low to high z score. The voxels displayed have z values exceeding the significance threshold of 3.10 with a Bonferroni correction for multiple comparisons ($p < 0.05$). VAC = vertical line passing through the anterior commissure; VPC = vertical line passing through the posterior commissure; BA = Brodmann area; L = left hemisphere; R = right hemisphere.

Discussion. *Control subjects.* Several important findings within the healthy subjects merit discussion.

This is, to our knowledge, the first PET study comparing motor imagery with the left versus the right hand. Only one functional MRI study investigated motor imagery with the right versus the left hand in normal subjects; it found activation of the primary motor cortex (30% of the activation during actual execution), lateral premotor cortex, and SMA.¹² The activation pattern was identical whatever the hand involved in task realization. Such a similar activation profile was also noted in a SPECT study during actual execution of a motor task with either the left or the right hand.³⁵

In the current study, motor imagery with the non-dominant hand was associated with most of the areas implicated in motor preparation, which is consistent with previous motor imagery studies with the right (dominant) hand.^{8,11,13} Some important similarities exist between left and right hand motor imagery. This is particularly the case for the lateral premotor cortex and cerebellum, which were activated irrespective of the hand, in accordance with previous work.^{10,15,17,36,37} However, some differences were found in the cerebral activation profile, depending on the hand with which subjects imagined the task. Indeed, a bilateral, instead of contralateral, activation was disclosed in the SMA and superior parietal lobe for left hand but not for right hand motor imagery. In addition, an ipsilateral activation of the DLPFC and inferior frontal gyrus was detected only with nondominant hand motor imagery. Conversely, the involvement

of the contralateral primary motor cortex was found during motor imagery only with the right hand. This asymmetry of cerebral activation may reflect the difficulty in imagining the task with the nondominant hand, which may induce recruitment of multiple areas involved in motor preparation. Comparatively, motor imagery with the right hand may be easier and implicates more executive areas. This asymmetric activation profile is partially reversed in patients with PD with right-sided akinesia, as discussed below.

Previous studies have suggested that activation of the SMA during motor imagery is linked to the internally guided component of the task. Thus, the SMA is usually not activated when imagery tasks are externally guided.⁸ In our study, the motor sequence could, in some ways, be considered as self-guided: after the “go” signal, subjects generated the three components of the movement sequence and the final button press by internal guidance at their own rhythm. This could explain the activation of SMA during motor imagery with both hands.

Another interesting finding in the control group was the confirmation of the importance of the superior parietal lobe (BA 7) in mental motor tasks and motor preparation, in accordance with previous human PET^{13,37} as well as primate physiology studies.³⁸

One of the unexpected results of our study was the almost absent activation of basal ganglia in all conditions, which differs from findings of several studies that have reported activation of the basal ganglia during motor imagery.^{18,20} This result is probably related to our rest condition, which was, in fact, a

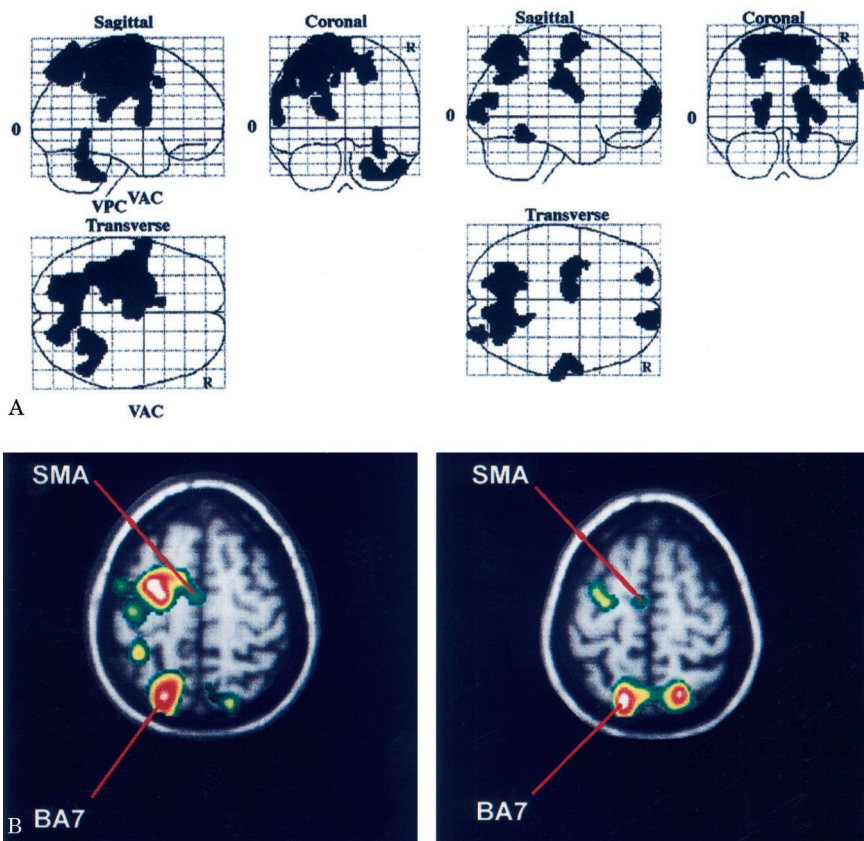


Figure 2. Motor imagery with the right hand versus rest condition. (A) Statistical parametric maps of increasing regional cerebral blood flow (rCBF) in the subtraction analysis (within-group study), showing the significantly activated areas for the control group (left panel) and the patients with PD (right panel). (B) The anterior supplementary motor area is activated in both groups. In control subjects, significantly increased rCBF (superimposed on an MR image of the brain) is noted in the left superior parietal lobe (BA 7). In patients with PD, this effect is seen bilaterally and no activation is noted in the contralateral primary motor cortex. VAC = vertical line passing through the anterior commissure; VPC = vertical line passing through the posterior commissure; BA = Brodmann area; L = left hemisphere; R = right hemisphere.

minimal motor condition. The purpose of such a rest condition was to duplicate the auditory and motor components of the imagery task, in particular the button press that signaled the end of the imagined sequence. Another important objective for the rest condition was to prevent the subject from inadvertently engaging in motor imagery. The problem of such a choice is that activation of basal ganglia could have appeared during our rest condition. This could explain why, after subtraction of the rest condition from the motor imagery condition, activation of basal ganglia may have been suppressed.

Patients with PD. One of the most important findings of this study is that the activation pattern in patients with PD compared with controls was already abnormal during motor imagery with the left (nonakinetic) hand. First, cerebral activation was globally reduced during left motor imagery compared with controls, as illustrated in figure 1A. Second, the SMA, which is preferentially deafferented in patients with PD, was not activated, although akinesia was minimal on the left side. This could reflect a more severe disruption of motor preparation in comparison with motor execution. These motor imagery abnormalities suggest that the physiologic processes underlying motor imagery are very sensitive to dopaminergic dysfunction and are thus less “lateralized” than those for motor execution and might be perturbed even when akinesia is mild. This seems of

Table 3 Sites of activation in patients with PD during motor imagery (z score > 3.10)

Activated areas	L/R	z Score	Stereotactic coordinates		
			x	y	z
Left hand					
Inferior frontal gyrus (BA 45)	L	3.47	-54	32	16
Anterior cingulate cortex	L	3.5	-16	34	-6
DLPFC (BA9)	L	3.25	-18	58	-2
Superior parietal lobe (BA 7)	R	4.3	30	-74	56
	L	5.5	-18	-68	62
Occipital cortex (BA 19)	R	3.36	32	-72	36
Right hand					
Primary motor cortex (BA4)	R	3.26	66	-18	34
SMA (BA6)	L	3.45	-6	-8	68
Lateral premotor cortex (BA6)	L	3.73	-26	-10	58
DLPFC (BA9)	R	4.36	18	68	12
Superior parietal lobe (BA 7)	L	5.15	-16	-70	62
	R	4.99	18	-64	60
Occipital cortex (BA 18)	R	3.1	32	-92	2
	L	3.11	-16	-82	16

BA = Brodmann's area; DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area.

major importance, because motor imagery represents an internal representation of action without any external guidance and thus is the typical kind of motor task with which patients with PD experience the most important difficulties.³⁹

When motor imagery was performed by patients with PD with the right (akinetetic) hand, an activation of the SMA was noted, in contrast to what was observed with the left hand. Conversely, the contralateral primary motor cortex and the inferior parietal lobe were not activated. Indeed, the activation profile was much more extended when the patients had to imagine the task with the right (dominant, but akinetic) hand rather than with the left (nondominant, but nonakinetetic) hand. This concerns in particular the SMA and ipsilateral primary motor cortex, which were activated only during right motor imagery, as if the dominance effect described in controls was reversed by the consequences of akinesia. The diffusion of activation noted ipsilaterally in the primary motor cortex and bilaterally in the superior parietal lobe during motor imagery with the right (akinetetic) hand may be considered as a compensatory mechanism, as already described for motor execution.^{21,22} Motor imagery abnormalities in patients with PD seem to be dependent on the hand with which they imagine the task, and the a priori hypoactivation of the SMA is not constantly found.

In a recent preliminary study, the effect of apomorphine, a potent dopaminergic agonist, on motor imagery abnormalities in patients with PD was investigated.⁴⁰ The task was externally paced and consisted of a sequential finger-to-thumb opposition movement performed with the right hand. One of the main findings of the study was preserved activation of the SMA independent of the condition (on and off apomorphine). Our data support these results, but only for motor imagery with the right (akinetetic) hand. Moreover, our findings suggest that SMA activation depends on the hand with which subjects imagine the movement.

Evaluation of the effect of the severity of akinesia on brain activation abnormalities during motor imagery could be the subject of future work in patients with PD with advanced illness surgically treated by deep brain stimulation by comparing on and off stimulation states.

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Obstructive sleep apnea is common in medically refractory epilepsy patients

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Article abstract—*Background:* Previous reports have documented the coexistence of obstructive sleep apnea (OSA) and epilepsy and the therapeutic effects of treatment on seizure frequency and daytime sleepiness. The authors' objective was to determine the prevalence of OSA and its association with survey items in a group of patients with medically refractory epilepsy undergoing polysomnography (PSG). *Methods:* Thirty-nine candidates for epilepsy surgery without a history of OSA underwent PSG as part of a research protocol examining the relationship of interictal epileptiform discharges to sleep state. Subjects also completed questionnaires about their sleep, including validated measures of sleep-related breathing disorders (Sleep Apnea Scale of the Sleep Disorders Questionnaire [SA/SDQ]) and subjective daytime sleepiness (Epworth Sleepiness Scale [ESS]). *Results:* One-third of subjects had OSA, defined by a respiratory disturbance index (RDI) \geq 5. Five subjects (13%) had moderate to severe OSA (RDI > 20). Subjects with OSA were more likely to be older, male, have a higher SA/SDQ score, and more likely to have seizures during sleep than those without OSA ($p < 0.05$). Seizure frequency per month, the number or type of antiepileptic drugs (AED) prescribed, the localization of seizures (temporal versus extratemporal), and the ESS were not statistically different between the two groups. *Conclusions:* In our sample, previously undiagnosed obstructive sleep apnea was common, especially among men, older subjects, and those with seizures during sleep. The impact of treating OSA on seizure frequency and daytime sleepiness in medically refractory epilepsy patients warrants further controlled study.

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Sleep disorders and epilepsy are common, treatable conditions. Unrecognized sleep-disordered breathing has been estimated to affect up to 24% of men and 9% of women,¹ with multiple case series documenting its coexistence with epilepsy.^{2–5} These reports

have also documented an improvement in seizure control, daytime sleepiness, or both when obstructive sleep apnea (OSA) is treated. These therapeutic benefits are particularly relevant in patients whose seizures persist despite treatment with antiepileptic

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drugs (AED) or who require sedating doses of AED to achieve seizure control. The prevalence of OSA in such patients with medically refractory epilepsy, however, has not been established. In addition, the clinical features associated with OSA in this population are not well characterized.

We report a high prevalence of OSA among a group of medically refractory epilepsy patients undergoing polysomnography (PSG). These subjects were participating in a sleep protocol examining the relationship of interictal epileptiform discharges (IED) to sleep state. The first night of PSG used to screen for sleep disorders, including sleep apnea; the second night of PSG was used to determine the relationship of IED to sleep. Subjects were selected for study because they were candidates for epilepsy surgery, rather than because of sleep-related complaints. As part of the protocol, subjects also completed questionnaires about their nighttime sleep, sleep-related breathing, and daytime sleepiness. This enabled us to assess the usefulness of survey responses in combination with clinical characteristics for predicting those at risk for sleep-disordered breathing.

Methods. *Subjects.* All subjects undergoing presurgical evaluation in the University of Michigan Epilepsy Laboratory between December 1995 and February 1997 and who met study criteria were asked to participate in the sleep protocol. Fifty-two percent agreed, for a subsample of 26 subjects. The most common reasons for not participating were being unable to miss work or arrange for childcare or transportation. An additional 13 subjects undergoing presurgical evaluations and meeting study criteria were recruited before December 1995 (as part of a pilot study on the effects of sleep on IED) or after February 1997 (as part of a follow-up study on the effects of sleep on IED in extra-temporal epilepsy). Some of these IED data have been previously reported.^{6,7} Participants met the following criteria: aged 18 to 65 years; ability to give informed consent; a history of recurrent unprovoked complex partial seizures, with at least one seizure in the last month; ictal semiology and long-term monitoring (LTM) consistent with complex partial seizures; no history of psychogenic seizures; no prior epilepsy surgery; and no recent medication discontinuation. Subjects were on constant doses of AED for at least 2 weeks before study. No subjects had been previously diagnosed with OSA. The primary goal of the two-night sleep research protocol was to assess the relationship between IED and sleep state. Comprehensive PSG was performed on the first night of study to obtain information about the subjects' sleep quality and to detect any unrecognized sleep disorders that might confound the results of the IED analysis. The protocol was approved by the University of Michigan Institutional Review Board.

PSG. PSG was performed in all 39 subjects in the University of Michigan General Clinical Research Center. Overnight recordings were performed on 21-channel polygraphs or 32-channel computerized EEG systems (Grass-Telefactor Corp., West Conshohocken, PA) and EEG, electro-oculogram, submental EMG, nasal-oral airflow, respiratory effort, pulse oximetry, and anterior tibialis EMG

were recorded. In our laboratory, an apnea is defined by a decrease in airflow or effort to 20% or less of baseline for 10 or more seconds. A hypopnea is defined by any decrease in airflow or effort for 10 or more seconds that is accompanied by either EEG signs of arousal (defined by the American Academy of Sleep Medicine criteria⁸) or a 4% or greater decrease in oxygen saturation. The respiratory disturbance index (RDI) is calculated by dividing the number of apneas and hypopneas by the total number of hours asleep. OSA was defined by an RDI \geq 5.⁹ Studies were scored by trained PSG technologists and reviewed by the first author (BAM).

Questionnaire data and medical record review. Questionnaire data included: 1) The Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA/SDQ),¹⁰ a validated measure of sleep apnea (see Appendix); 2) The Epworth Sleepiness Scale (ESS), a validated measure of subjective daytime sleepiness which assesses the likelihood of a subject to fall asleep in certain situations, such as watching television¹¹; 3) Information on seizure frequency, and whether seizures occurred during sleep. Those reporting seizures during sleep either part of the time or most of the time (as opposed to rarely or never) were classified as having seizures during sleep. The SA/SDQ is a 12-item survey with total scores ranging from 0 to 60. Using receiver-operating characteristic curves, cutoff points for apnea of 36 for men and 32 for women have been suggested, although these cutoffs await confirmation in larger scale studies.¹⁰ The ESS is an eight-item scale with total scores ranging from 0 to 24, with an ESS score greater than 10 generally regarded as consistent with excessive daytime sleepiness.¹¹

A proportion of subjects completed the protocol before we began giving the SDQ and ESS routinely. Therefore, SA/SDQ scores were available for 28 subjects, ESS scores were available for 34 subjects, a history of loud snoring or witnessed apnea was available for 36 subjects, and body mass index (BMI; weight in kilograms/height in meters squared) was available for 37 subjects. Information regarding seizure frequency and seizures during sleep was available for all subjects. Medical records were reviewed to obtain information regarding the number and type of anti-epileptic drugs (AED), other medications, type of seizure (complex partial, secondarily generalized, or both), localization of the epileptogenic region (temporal versus extra-temporal; based primarily on LTM results and also on brain imaging), whether treatment was prescribed for OSA, and follow-up in those who were treated. Levels of AED were available in the majority of subjects (29 out of 39) for phenytoin, carbamazepine, valproate, mysoline, and phenobarbital, but not for lamotrigine or gabapentin. Therapeutic ranges were 10 to 20 mg/L for phenytoin, 4 to 12 mg/L for carbamazepine, 40 to 100 mg/L for valproate, 4 to 12 mg/L for mysoline, and 15 to 40 mg/L for phenobarbital.

Statistical analysis. For all statistical tests, the level of significance was set at $\alpha = 0.05$. All statistical tests were performed using the SPSS statistical analysis package (SPSS Inc, Chicago, IL). Major predictor variables between subjects with OSA and those without were compared using two-tailed independent sample *t*-tests for continuous data, and χ^2 or Fisher's Exact tests for categorical data. Continuous variables included age, seizures per month, the number of AED, the total SA/SDQ score, BMI,

Table 1 Characteristics of subjects with obstructive sleep apnea (OSA)

Subject no.	Age, y/sex	RDI	mO ₂	Antiepileptic drugs	Treatment of OSA	Treatment outcome
1	40/M	61.2	83	PHT, PRM, GBN	Yes, after surgery	Improvement in daytime alertness with CPAP but poor compliance after 1 y
2	46/M	32.2	87	CBZ	Yes, after surgery	Did not tolerate CPAP
3	30/M	23.6	90	PHT	Yes, after surgery	Tolerating oral appliance well with improved daytime alertness
4	35/M	23.0	84	PHT, VPA	Yes, after surgery	Improvement in daytime alertness with CPAP but poor compliance after 1 y
5	24/M	20.5	87	PHT, LTG	Yes, before surgery	Did not tolerate CPAP
6	45/M	5.0*	87	PHT, VPA	Yes, after surgery	Improved CPAP use after retitration and nasal pillows added; improved daytime alertness
7	54/F	8.9	91	PHT, LTG	No	—
8	46/M	8.3	90	VPA, LTG	No	—
9	43/M	8.0	79	CBZ, GBN	No	—
10	48/F	7.4	89	PHT	No	—
11	39/F	6.7	88	CBZ, LTG	No	—
12	44/F	6.0	89	VPA, LTG	No	—
13	24/M	5.7	90	CBZ	No	—

* Repeat RDI 1 year later was 31.7.

RDI = respiratory disturbance index (number of apneas and hypopneas per hour of sleep); mO₂ = minimum oxygen saturation; PHT = phenytoin; PRM = primidone; GBN = gabapentin; CPAP = continuous positive airway pressure; CBZ = carbamazepine; VPA = valproic acid; LTG = lamotrigine; TPM = topiramate.

and ESS score. Categorical variables included gender; AED type (presence or absence of phenytoin, carbamazepine, valproate, lamotrigine, or gabapentin); presence of secondarily generalized tonic-clonic seizures; presence of additional medication having sedating effects or effects on upper airway tone; localization of the epileptogenic region (temporal versus extratemporal); a history of seizures occurring habitually during sleep either part of the time or most of the time (as opposed to rarely or never); and self-reported loud snoring or witnessed apneas occurring occasionally, often, or almost always (combined into one response as subjects rarely reported being told that they had apnea). Seizures per month were also grouped into those with 10 or more seizures per month and those with fewer than 10 seizures per month. Predictor variables were also compared within logistic regression models.

Results. *Univariate and bivariate analyses.* Thirteen (33%) of 39 subjects had respiratory disturbance indexes (RDI; apneas and hypopneas per hour) of 5 or greater (OSA group; table 1). In seven of the 13 subjects, the sleep-related breathing disorder was mild (RDI < 10) and continuous positive airway pressure (CPAP) or other treatments were not initiated. In five subjects (13%), the degree of OSA was moderate to severe (RDI > 20), and CPAP was initiated. In one subject (Subject 6), who had an initial RDI = 5, repeat testing was performed 1 year later, after he had gained 20 pounds. His repeat testing showed an RDI = 31.7, and CPAP was initiated.

Differences between the OSA group and the group without OSA for major predictor variables are listed in table 2. On average, subjects in the OSA group were older, and a

higher proportion were men. A higher proportion reported seizures during sleep. The total SDQ score and specific subitems within this scale, including BMI and loud snoring or witnessed apneas, were higher or more frequent in the OSA group. Localization of the epileptogenic region (temporal versus extratemporal) and seizure frequency per month (analyzed both as a continuous variable and as a categorical variable of 10 or greater seizures per month versus fewer than 10 seizures per month) did not differ significantly between the groups.

The number or type of AED prescribed did not differ significantly between the groups. In five subjects, all on phenytoin, levels were above the therapeutic range but still within the range used to treat refractory seizures (26 to 29.3 mg/L). Two of these five subjects had OSA. Fourteen subjects were taking additional medications, which included antidepressants (eight subjects), antihypertensive or cardiac agents (five subjects), asthma inhalers (two subjects), histamine receptor blockers for gastroesophageal reflux (one subject), antipsychotic medication (one subject), and hormone replacement therapy (three subjects; e.g., thyroid, estrogen, and progesterone). Groups did not differ in the number of subjects taking antidepressants, which may have sedating effects and also improve upper airway tone and reduce REM sleep.

The ESS scores did not differ significantly between the groups. Subjects reporting seizures during sleep had a higher total SDQ score than those not reporting seizures during sleep (26 ± 6.8 versus 20.2 ± 5.1 ; mean \pm SD; $p = 0.02$). However, BMI was not different between the subjects reporting seizures during sleep (26.9 ± 5.9) and those not reporting seizures during sleep (23.8 ± 4.5 ; $p = 0.09$).

Table 2 Differences between subjects with and without obstructive sleep apnea (OSA)

Characteristic	OSA, n = 13	No OSA, n = 26	p Value
SA/SDQ score, mean \pm SD	28.9 \pm 7.2	21.3 \pm 5.1	0.003
Loud snoring or witnessed apnea, n (%) [*]	8 (62)	6 (23)	0.01
Body mass index, mean \pm SD	28.6 \pm 7.1	24.3 \pm 4.2	0.03
Age, y, mean \pm SD	39.9 \pm 9.2	32.9 \pm 9.9	0.04
Male sex, n (%)	9 (69)	9 (35)	0.04
Seizures during sleep, n (%)	10 (77)	11 (42)	0.04
Temporal localization, n (%)	11 (85)	25 (81)	0.76
Seizures/mo, n, mean \pm SD	12.1 \pm 15.0	10.8 \pm 12.1	0.77
Antiepileptic drugs, n, mean \pm SD	1.69 \pm 0.6	1.50 \pm 0.6	0.60
Epworth Sleepiness Scale score, mean \pm SD	7.3 \pm 3.6	6.0 \pm 3.6	0.33
Secondarily GTCS, n (%)	5 (38)	8 (31)	0.63
Subjects taking antidepressant medications, n (%)	3 (23)	5 (19)	0.54

Boldface indicates significant characteristics.

* Defined as occasionally, often, or almost always.

SA/SDQ = Sleep Apnea Scale of Sleep Disorders Questionnaire; GTCS = generalized tonic-clonic seizure.

Multivariable analysis. A logistic regression model containing the total SDQ score and gender was constructed to compare the effects of these variables on OSA. The total SDQ score remained a predictor of apnea (OR for a 5-point increase in SA/SDQ score = 3.0; $p = 0.02$), and gender was not a predictor (OR = 1.14; $p = 0.89$). A preliminary model had shown that SDQ score was a stronger predictor of OSA (OR for a 5-point increase in SA/SDQ score = 2.3; $p = 0.08$) than the presence of seizures during sleep (OR = 0.00007; $p = 0.84$). Because seizures during sleep were correlated with SDQ score and because age, BMI, and loud snoring or witnessed apneas were already incorporated into the SDQ (and therefore correlated with the total SDQ score), these variables were not included in the final model.

Clinical outcome. Six subjects with OSA were treated, one before epilepsy surgery (see table 1). The other five subjects wished to defer their treatment until after epilepsy surgery had been performed. One subject (Subject 3) is using an oral appliance with improved daytime alertness and has been seizure-free after surgery. The other five subjects who were treated with CPAP have had variable responses. Two subjects (Subjects 1 and 4) initially tolerated the device for 1 year with improved daytime alertness but were not compliant with CPAP long-term; both have postoperative seizures. Another subject (Subject 6), initially intolerant of CPAP, underwent a repeat titration and replacement of the mask with nasal pillows. He has been using CPAP successfully for the last year and notes improved daytime alertness even after topiramate was added to control postoperative seizures. Two others did not tolerate CPAP; one is seizure-free (Subject 2) and the other (Subject 5) had sudden unexplained death several weeks after epilepsy surgery, presumably due to a postoperative seizure.

Discussion. Our results indicate that OSA is common among subjects with medically refractory sei-

zures. One-third of subjects had an RDI \geq 5, indicating mild OSA, and 13% of subjects had an RDI $>$ 20, indicating moderate to severe OSA. In addition, we found that OSA was associated with increasing age, male gender, seizures during sleep, and SA/SDQ score, but not with seizure frequency or type, AED number or type, antidepressant use, seizure localization, or ESS score. The prevalence of OSA in our subjects was higher than that reported in a population-based study of adult state workers without epilepsy, in which 24% of men and 9% of women had an RDI \geq 5.¹ In our sample, 50% of men and 19% of women had an RDI \geq 5.

Our study is unique in that we performed PSG as part of a research protocol in a group of medically refractory epilepsy patients who were not previously diagnosed with OSA. Our subjects underwent PSG as part of an unrelated study examining the relationship of IED to sleep. In a retrospective review of epilepsy patients undergoing PSG in our laboratory, OSA was present in 45 (71%).⁵ However, these patients had been referred specifically for the evaluation of sleep disorders, including OSA.

Our results support the use of screening questions and questionnaires related to sleep-disordered breathing in assessing epilepsy patients for OSA. Although most subjects did not report having been told that they stopped breathing during sleep, many reported that they had been told they snored loudly. Loud snoring and an increased BMI were associated with OSA; OSA was also higher in men. The strongest predictor of OSA was the SA/SDQ, a self-administered screening questionnaire that incorporates self-reported loud snoring or witnessed apnea, BMI, smoking, a history of hypertension, and other factors (see Ap-

pendix). Our findings are congruent with studies of predictors of OSA in the general population. The strongest predictors of OSA are obesity and male gender.¹² Other risk factors include craniofacial features, genetic factors, and environmental exposures that increase airway inflammation (e.g., smoking) or decrease neuromuscular output to the upper airway (e.g., alcohol or sedatives). Young's study of adult state workers in Wisconsin identified male gender, obesity, and habitual snoring as factors strongly associated with OSA.¹ Men were 2.0 to 3.7 times more likely than women to have sleep-disordered breathing. An increase in one SD in any measure of body habitus, including BMI, translated into a threefold increased risk of sleep-disordered breathing.

In contrast to the SDQ, the ESS, a measure of subjective daytime sleepiness, did not differ among subjects with and without OSA. There are several possibilities for this lack of sensitivity. First, not all subjects with OSA have daytime sleepiness. In the study of sleep-disordered breathing in adult state workers in Wisconsin, 9% of women and 24% of men had an RDI ≥ 5 . However, only 2% of women and 4% of men had OSA syndrome, defined as an RDI ≥ 5 and daytime hypersomnolence.¹ Second, subjects with epilepsy may be sleepy for other reasons besides OSA, including AED effects, seizures, or the effects of seizures on sleep.^{13,14} Finally, subjects may underestimate their degree of daytime sleepiness or may change their lifestyle to compensate over time for decreased alertness.⁹

The reasons why the prevalence rate of OSA was so high in our sample as compared with non-epilepsy patient populations are uncertain. One possibility is that AED influence OSA. Barbiturates and benzodiazepines, and weight gain in patients treated with valproate, may precipitate or exacerbate OSA.^{15,16} Although no association was found between OSA and AED number or type, our subjects were taking a variety of medication combinations, and the number taking any given AED was relatively small. Only one of three subjects on sedative AED (phenobarbital, misonal, or clonazepam) had OSA. Two of five subjects with supertherapeutic AED levels had OSA. Larger studies will be necessary to determine whether specific AED regimens exacerbate OSA, whether supertherapeutic AED levels influence OSA, and whether patients with medically refractory seizures have a higher prevalence of OSA than those with controlled seizures, or those without epileptic seizures.

The association of OSA with seizures during sleep in our series is intriguing. We previously reported in abstract form that subjects with seizures during sleep were more likely to have OSA as compared with those with seizures during wakefulness.¹⁷ However, we cannot determine from our data whether subjects reporting seizures during sleep were more likely to have OSA for other reasons, such as a higher prevalence of obesity, or whether OSA was causal in facilitating seizures during sleep. Subjects reporting seizures during sleep showed a trend to-

ward a higher BMI, but this was not statistically significant. Alternatively, several case series have documented an improvement in seizure control with treatment of OSA, implying that OSA may facilitate seizures.²⁻⁵ A variety of seizure-provoking mechanisms have been proposed. Cerebral hypoxemia, decreased cardiac output, and cardiac arrhythmias seem unlikely, given that we have not encountered any examples of epileptic seizures resulting from acute cardiopulmonary changes in our sleep laboratory population in the last 15 years.⁵ Other proposed mechanisms include sleep deprivation and fragmentation of sleep with frequent stage shifts, arousals, and entries into sleep after arousal. If sleep deprivation is the assumed mechanism, one might expect that seizures during both sleep and wakefulness would be facilitated in patients with epilepsy with OSA. In contrast, if sleep fragmentation and frequent stage shifts resulting from apneas are responsible for provoking seizures, then seizures during sleep may be facilitated preferentially in patients with epilepsy with OSA. These proposed mechanisms await further experimental investigation.

Poor compliance with CPAP, the first-line treatment for OSA, is a commonly recognized problem that is not unique to our subjects.¹⁸ Many patients find it cumbersome to use CPAP equipment nightly. In one study, simple interventions were found to improve CPAP compliance.¹⁹ These interventions include providing written educational materials and contact with patients in the first few weeks after treatment is initiated to troubleshoot problems and encourage use. A variety of surgical techniques are available for those with OSA who are not able to tolerate CPAP, although the success rate of surgery is not as high as with CPAP. Nonsurgical alternatives to CPAP treatment for mild to moderate OSA include weight loss, positional therapy to avoid the supine position, avoidance of alcohol, and oral appliances.⁹

We cannot comment on the effects of OSA treatment on seizure control and daytime sleepiness in our sample because only a few subjects were treated. Although case series have suggested that treating OSA is beneficial for seizure control and for improvement of daytime sleepiness, randomized clinical trials will be necessary to definitively answer this question and to identify those patients in whom seizures will respond to treatment. A relevant question is whether subjects with mild OSA (RDI between 5 and 20), as compared with those with more severe OSA, may benefit from treatment. If seizures, daytime sleepiness, or both respond to treatment of even mild OSA, it may be worth the effort and expense necessary to diagnose and treat all patients with epilepsy presenting with symptoms of sleep-disordered breathing. Further investigations of sleep-disordered breathing in patients with epilepsy may also enhance our understanding of the mechanisms whereby sleep disorders, and their treatment, affect seizure control.

Appendix

Sleep Apnea Scale of the Sleep Disorders Questionnaire

1. I am told I snore loudly and bother others.
2. I am told I stop breathing ("hold my breath") in sleep.
3. I awake suddenly gasping for breath, unable to breathe.
4. I sweat a great deal at night.
5. I have high blood pressure (or once had it).
6. I have a problem with my nose blocking up when I am trying to sleep (allergies, infections).
7. My snoring or my breathing problem is much worse if I sleep on my back.
8. My snoring or breathing problem is much worse if I fall asleep right after drinking alcohol.
9. What is your current weight? (Five categories)
10. How many years were you a smoker? (Five categories)
11. How old are you now? (Five categories)
12. Body mass index (calculated from weight in kilograms/height in meters squared) (Five categories)

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