Striatal activation during blepharospasm revealed by fMRI

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Abstract—*Objective:* To investigate brain areas involved in the initiation and execution of eyelid spasm in patients with benign essential blepharospasm. *Methods:* The authors used fMRI and correlated the blood oxygenation level-dependent (BOLD) signal with epochs of frequent eyelid spasm in six patients and with epochs of voluntary eye blinks in four healthy subjects. *Results:* Spasm epochs were accompanied by activation in a subregion of the putamen in all patients, whereas voluntary blinking in healthy subjects was not. Other areas of activation common to patients and healthy subjects included frontal and parietal operculum, supplementary motor area, primary sensorimotor cortex, various visual areas, and the cerebellum. *Conclusions:* The striatum may be involved in the initiation or execution of eyelid spasm. Future studies, possibly including electromyography (EMG) during fMRI, are needed to detect the sequence and role of other concomitantly activated areas.

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Whereas secondary blepharospasm occurs after a variety of lesions in the upper brainstem and thalamus,[1-3] the lower pontine region,[4] and the basal ganglia,[5-7] usually no detectable lesion is present in patients with primary benign essential blepharospasm (BEB).[8,9] Clinical studies propose dysfunction in the basal ganglia as a cause of BEB.[9] Based on a rat model of the disease, it has been suggested that BEB may result from a combination of a subclinical lesion in the basal ganglia and an external ophthalmic insult.[10] PET studies[11,12] and an MRS study[13] also indicate abnormalities of basal ganglia functioning in patients with BEB. Another PET study describes hypoactivity in cortical areas controlling the eyelids and hyperactivity in the pons and cerebellum as possible causes of BEB.[14]

In this study, we use fMRI to determine activation patterns of BEB patients. We exploit the temporal resolution of fMRI to identify areas that show a close temporal relationship in their activity with episodes of frequent involuntary lid spasm. Guided by previous studies, we focus on the basal ganglia and thalamus.

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Materials and methods. FMRI was performed on six patients (two men, four women; five right-handed [Patients A, C, D, E, and F], one left-handed [Patient B]) with BEB and on four healthy control subjects (two men [Subject G, aged 25 years; Subject H, aged 56 years] and two women [Subject I, aged 31 years; Subject J, aged 67 years]). The local human subjects review committee approved the protocol of the study, and written informed consent was obtained from all patients and control subjects. Patients were selected from Blepharospasm Clinics at the Department of Ophthalmology of Frankfurt and Bonn universities. All patients experienced intermittent involuntary blinking involving both eyes with spasm-free intervals of several seconds to minutes.[15] No other neurologic or ocular diseases associated with or followed by blepharospasm were reported. Patients had no family history of focal dystonia or tremor. Blinking did not stop with change of posture and continued while lying in the scanner. Four patients were measured within a 3-month cycle of regular botulinum toxin injections into the eyelids (Patients B, C, E, and F). For details of clinical appearance and preceding treatment, see table 1.

We assessed blinking periods using two methods. The first protocol involved patients indicating the onset of a spasm episode by pressing a button of a fiberoptic answer box with the index finger and the offset by pressing another button with the middle finger (subjective reference). All patients and control subjects, except Patient C, were tested using their dominant hand. The second method was based on the detection of eye-blink frequencies using an infrared eye tracker (Ober2, Permobil Meditech, Timra, Sweden). This provided objective reference and helped to discrim-

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Table 1 *Patient history*

Patient/sex/age/onset	Severity	Treatment	Last BT injection
A1 M 48/46	Moderate, left eye more severely affected	q 3 months BT injections for 1 year	8 months before study
A2 M 50/46	No change	No treatment	—
B M 61/50	Moderate to severe, no lateralization	Initially benzodiazepines, antidepressants, psychosomatic therapy; q 3 months BT injections for 5 years	6 weeks before study
C W 67/63	Severe, no lateralization	q 3 months BT injections for 2 years	7 weeks before study
D W 32/15	Mild, no lateralization	No treatment	—
E W 63/55	Moderate to severe, no lateralization	q 3 months BT injections for 4 years	12 weeks before study
F W 54/51	Moderate to severe, right eye more severely affected	Artificial tears, 1 BT injection	5 weeks before study

BT = botulinum toxin; M = man; W = woman; evaluation of severity according to 15.

inate between neuronal activation induced by button pressing or blinking. However, because the eye tracker increased the noise level of MRI, this method was only used for two patients (Patients B and D). Sessions with both methods were obtained for Patient B and all healthy control subjects. For blink detection by thresholding, amplitudes of large vertical and horizontal saccades and blinks were individually evaluated before fMRI data acquisition. Blinks resulted in much larger signal amplitudes than saccades and thus could be easily extracted from the infrared traces monitoring vertical eye movements. Volumes of 2-second (for repetition time [TR] = 2 seconds) or 4-second (for TR = 4 seconds) duration containing two, four, or more blinks were defined as spasm episodes; volumes containing fewer blinks were defined as nonspasm intervals.

Healthy control subjects were instructed verbally to start blinking voluntarily every 10th volume (every 50.6 seconds) and to stop after a 5-volume duration (25.3 seconds). The infrared detector indicated eye blinks in one session, and the subjective button press noted eye blinks in a second session. We did not use voluntary blinks as a control condition in patients because of the frequent involuntary spasms and active countermovements that would make the interpretation of such fMRI data impossible.

The fMRI data were acquired using a 1.5-T Magnetom Vision MRI scanner (Siemens, Erlangen, Germany) using a gradient echo planar imaging (EPI) sequence for fMRI (echo time [TE] = 69 ms, flip angle [FA] = 90°, field of view [FOV] = 200 × 200 mm^2; for TR, voxel size, number of slices of the patients, see table 1; parameters of the control subjects: 24 slices, TR = 5 seconds, voxel size = 3.2 × 3.2 × 5 mm^3). Each scan comprised the acquisition of 128 volumes. An oblique acquisition plane (−10° to −20° from the anterior commissure [AC]–posterior commissure [PC] plane) was chosen to avoid sections through the eyes. A T1-weighted three-dimensional (3D) magnetization-prepared rapid acquisition gradient echo (MP-RAGE) scan was recorded for each session (TR = 9.7 ms, TE = 4 ms, FA = 12°, matrix = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm^3). Dim illumination was kept during scanning, and subjects were instructed to fixate a cross that was positioned at the top of the MR tube.

Data analysis, registration, and visualization were performed using the fMRI software package BrainVoyager 4.0 (Brain Innovation, Maastricht, The Netherlands). Based on the slice parameters of the MR tomograph, the two-dimensional (2D) functional data sets were aligned with the 3D data sets through a Cartesian coordinate transformation, finally yielding four-dimensional (4D) data representations (volume time course: 3 × space, 1 × time). The individual anatomic 3D data sets were transformed into Talairach space,[15,16] and the same transformation was performed for the volume time courses, which were also interpolated to a functional voxel size of 3 × 3 × 3 mm^3.

The spatial normalization into 3D Talairach space as implemented using the BrainVoyager software is based on the following steps:

1) The origin of the coordinate system is placed in AC, and the AC–PC line is defined as the y-axis. The line that traverses the AC in the interhemispheric (midsagittal) plane and is perpendicular to the AC–PC line is defined as the z-axis. The plane that passes through the AC–PC line and is perpendicular to the interhemispheric plane is defined as the AC–PC plane.
2) Determination of the cortical periphery as defined by the most anterior point of the frontal cortex and the most posterior point of the occipital cortex, the highest point of the parietal cortex and the lowest point of the temporal cortex, and the most lateral points of the parietotemporal cortex.
3) Based on these points and planes, 12 subvolumes of the cerebrum[16] are determined (left, right to the interhemispheric plane x above, below the AC–PC plane x anterior to AC, between AC and PC, and posterior to PC).
4) The transformation from the individual brain coordinates into the coordinates of the Talairach brain is done separately for each of the 12 subvolumes. This proportional grid system helps to localize reliably individual anatomic structures[17] because potential errors are confined to the respective subvolume.

Before statistical analysis, the time series of functional images were aligned to minimize the effects of head movements. The central volume of the time series was used as a reference volume to which all other volumes were registered using a 3D motion correction that estimates the three translation and three rotation parameters of rigid body transformation. The realigned time series were spatially filtered by convolution using a 3D Gaussian smoothing kernel with full width at half maximum (FWHM) = 4 voxels. In addition to the removal of linear drifts from each voxel's time course, temporal filtering was performed by convolution using a Gaussian smoothing kernel of FWHM = 2 volumes.

After these preprocessing steps, the cerebral regions with activation related to involuntary or voluntary blinks were identified using correlation analysis between the protocol of blinking periods and the fMRI signal.[18] The reference function in our analysis was a sequence of "0s" (during the rest periods) and "1s" (during the blinking period, as obtained from the infrared detection of eye blinks or the report by button press). For the sessions using infrared detection of eye movements, the reference function was shifted by one (for the TR = 4-second protocols) or two volumes (for the TR = 2-second protocols) to account for the hemodynamic delay. For the button-press conditions, the reference function was convolved with a model function of the hemodynamic response[19] that considers the ideal time course of blood oxygenated level-dependent (BOLD) activity after a sensory or motor event (in this case, the button press). The 3D correlation maps from the application of these reference functions to the volume time courses were thresholded, and clusters of contiguous suprathreshold voxels were color coded in the images (figure 1).

A uniform threshold could not be applied to the 3D correlation maps because noise levels varied between patients and between

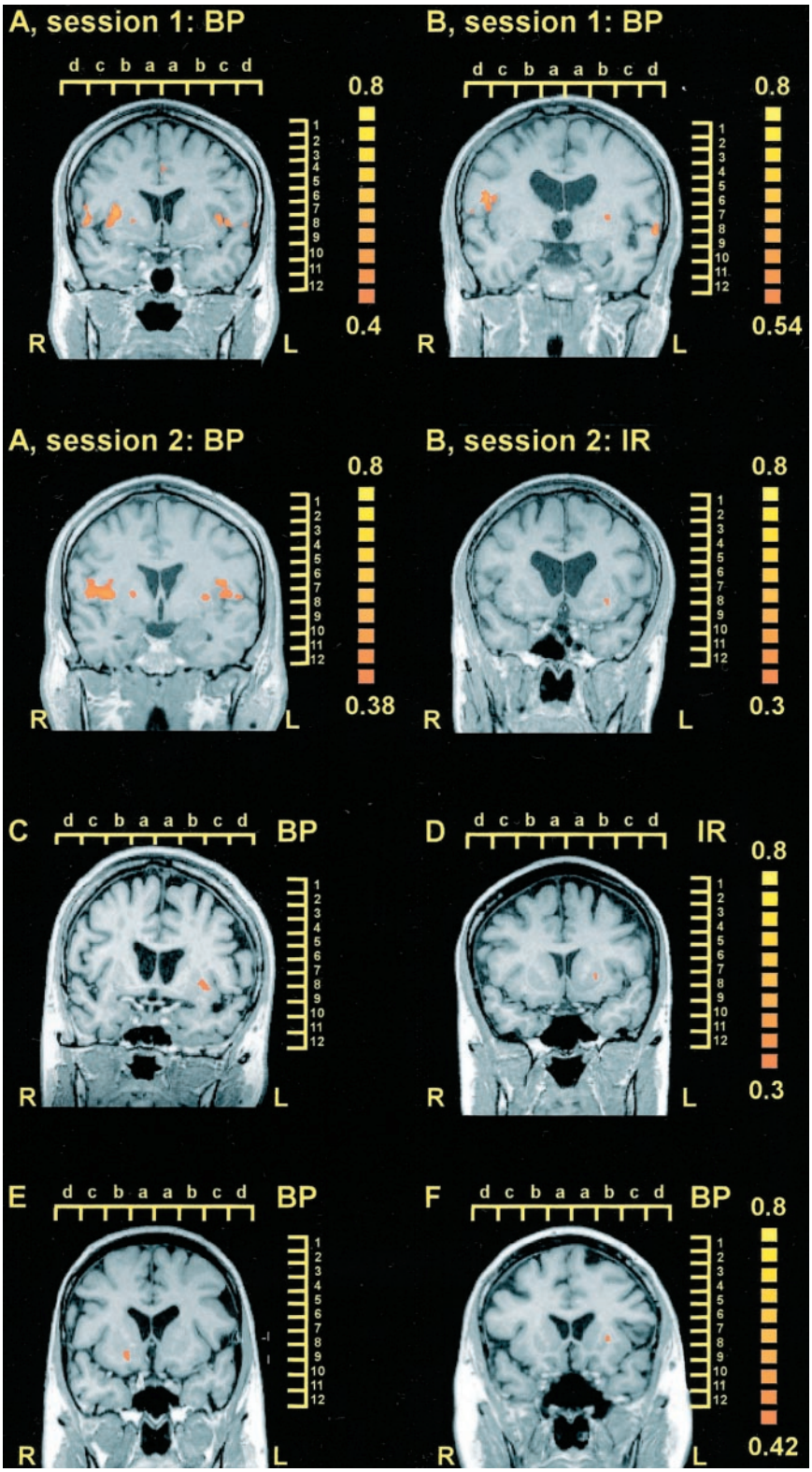

Figure 1. Putamen activations in six patients during episodes of frequent eyelid spasms indicated by button press or infrared detection. Functional data superimposed on coronal MRI slices in Talairach space[16] through the centroid of the putamen activation on the right in Patients A and E and on the left in Patients B, C, D, and F. Numbers and letters according to the proportional grid system of the Talairach atlas are given for better orientation in the images. For Talairach coordinates, see table 2. The correlation coefficient is color coded on the right referring to pictures in one row in C through F. BP = button press reference; IR = infrared detected reference; R = right; L = left. (A) Cerebral activation pattern for Patient A during the first measurement (A1; A, session 1) and the retest measurement (A2; A, session 2) 2 years later. Note that the right putamen is activated during both sessions (A1, ab78; A2, ab78), and the left putamen is activated during A2 (bc8). Other areas activated during both sessions include the frontal operculum bilaterally (right cb78 and left cd78), which can be attributed to the button press and activation in the cingulate gyrus during A1 (a45). (B) Cerebral activation of Patient B during session B1 (B, session 1) with button press and during session B2 (B, session 2) with infrared detection. The putamen area is activated during subjective (B1, b78) and objective (B2, b8) sessions. Note that activation in the right operculum is present during session 1 with button press (dc67) but not during session 2 without button press but with infrared detected reference. (C through F) Coronal MRI slices in Talairach space with superimposed functional data of Patients C, D, E, and F showing unilateral putamen activation during involuntary spasms with button press (C, E, F) or infrared detection (D).

healthy subjects and increased with the presence of the infrared eye position system in the scanner. For patients, correlation thresholds and minimal cluster sizes were adjusted to a level where correlated BOLD signals were first detectable in the region of interest (ROI; basal ganglia), assuming a minimal corrected significance level of 5% (table 2). In healthy subjects, correlated BOLD signals above noise level were never found in the basal ganglia. Thus, correlation thresholds were uniformly adjusted to a correlation coefficient of 0.5 for the button-pressing data sets. Because data quality varied with the infrared eye monitoring system, thresholds in the infrared data sets of healthy subjects were adjusted to a level at which primary sensorimotor cortex and cerebellum activation were detectable. *p* Values of the obtained correlation coefficients (given 128 time points per measurement) of all activated areas were corrected for multiple comparisons using the overall number of functional voxels of the measured intracranial volume and, for an ROI analysis,[20] an estimate of voxels representing the basal ganglia and the thalamus based on the coordinates of the atlas of Talairach and Tournoux[16] (see table 2).

In Patients B and D, inferior frontal activation that extended

Table 2 *Imaging parameters and activation in the putamen*

Experiment	Reference function	No. of slices	TR (s)	Voxel size (mm^3)	x	y	z	r	p (corrected)	p (ROI-corrected)	Cluster size (AV; 1 mm^3)
A1 (42517 FV)	BP (r)	15	4	$1.6 \times 1.6 \times 3$	19	3	9	0.52	1.67×10^{-5}	1.4×10^{-6}	39
A2 (29054 FV)	BP (l)	12	2	$3.2 \times 3.2 \times 3$	20	−2	9	0.54	2.1×10^{-6}	2.6×10^{-7}	37
					−28	−1	7	0.55	9.27×10^{-7}	1.2×10^{-7}	73
B1 (55550 FV)	BP (l)	12	2	$3.2 \times 3.2 \times 3$	−28	−6	8	0.67	9.26×10^{-13}	4×10^{-14}	88
B2 (29586 FV)	IR	12	4	$3.2 \times 3.2 \times 3$	−28	10	0	0.41	0.074	0.009	68
C (71264 FV)	BP (l)	16	4	$1.6 \times 1.6 \times 5$	−31	1	0	0.43	0.036	0.001	168
D (63253 FV)	IR	15	4	$1.6 \times 1.6 \times 4$	−18	10	5	0.5	1.96×10^{-6}	10^{-5}	21
E (61152 FV)	BP (r)	24	4	$3.2 \times 3.2 \times 5$	19	10	−4	0.45	0.008	4.6×10^{-4}	37
F (59575 FV)	BP (r)	24	4	$3.2 \times 3.2 \times 5$	−24	16	5	0.57	2.8×10^{-8}	1.7×10^{-9}	97

Raw p-values are corrected (p, corrected) for multiple comparisons within the entire intracranial functional data set (FV in the first column = number of intracranially located functional voxels) or within the region of interest (ROI) containing thalamus and basal ganglia (3666 FV; ROI-corrected). Note: except for B2, all activations are significant within the entire data set; x, y, z triples are the Talairach coordinates of activation peaks and r is the correlation coefficient.

BP = button press; IR = infrared detection; r = right hand button press; l = left hand button press; FV = functional voxel ($3 \times 3 \times 3$ mm^3); AV = anatomical voxel ($1 \times 1 \times 1$ mm^3).

into the orbit and exceeded a 10% signal increase had to be rejected as probable eye movement artifact.

Results. None of the subjects had cortical or subcortical lesions or indications of subcortical sclerosis or vascular pathology on MRI. The filtered time courses of the BOLD signal were correlated with reference time courses reconstructed from the infrared detection or the button-press reference, or both (see Methods). All six patients showed correlations that met the significance criterion of 5% between the BOLD signal in the putamen and episodes of increased blink frequency (see figure 1 and table 2; $r > 0.4$). The size of the activated region at threshold was 21 to 168 anatomic voxels (70.5 ± 49 mm^3).

The putamen focus was the only activation that differed consistently from that observed with voluntary blinking in healthy subjects. In contrast to patients, none of the healthy subjects revealed any basal ganglia or thalamus activation that correlated with periods of voluntary eye blinks (significance criterion, 5%). During instructed voluntary blinking, all healthy subjects consistently revealed mostly bilateral clusters of significantly correlated activation (significance criterion, 5%) in the primary sensorimotor cortex, supplementary motor area, frontoparietal operculum, striate and extrastriate visual cortex, and cerebellum with and without concomitant button pressing.

In all these areas, BOLD signal time courses correlated significantly with involuntary lid spasms in patients. The primary sensorimotor cortices were only included in the measurements of Patients C, D (infrared detection), E, and F and contained significant clusters during button-press protocols. The cerebellum was included in measurements of Patients C, E, and F and revealed suprathreshold voxel clusters only in Patients E and F. As with the healthy subjects, clusters of significant activation were found in the frontoparietal operculum of Patients A (1/2; see figure 1A, sessions 1 and 2) and B (button press; see figure 1B, session 1), the supplementary motor area of Patient A (1), and in the extrastriate visual cortex of Patients B and F.

Further activations in the patient group that were not observed during voluntary blinking and button pressing of control subjects included the parietooccipital sulcus and inferior frontal gyrus in Patients A (1/2) and D, the cingulate gyrus in Patients A (1/2) and B, and the insula in Patient B. The superior temporal gyrus was activated in Patient B and Subjects G and I. The explanation for this response is unknown because it occurred only in some of the control subjects (who all received auditory instruction) and also in one of the patients (who did not).

To test whether spasm-related putamen activation was reproducible during progress of the disease, Patient A was retested after 2 years. Spasm-related activity was found in the right putamen during the first session (see figure 1A, session 1). The retest session confirmed this activation and additionally revealed spasm-related activity in the left putamen at the same significance level (see figure 1A, session 2). However, lowering the threshold revealed that weak activity in the left putamen had been present also during the first session. All other patients displayed unilateral activation patterns of the putamen mostly ipsilateral to the hand used for button press (except Patient F) without lateralization of the lid spasms (see figure 1). Patient B was tested with subjective button press and passive monitoring of eye blinks in two consecutive sessions (see figure 1B) and additionally confirmed that activation of basal ganglia was not related to the button press itself. With button-press reference (see figure 1B, session 1), we found a strong correlation of episodes of high lid spasm activity with hyperactivity in the left putamen (see table 2; $p < 10^{-6}$, corrected) and in the right frontal operculum. When correlating with an objectively obtained reference time course of spasm episodes (see figure 1B, session 2), hyperactivity in the left putamen remained (time course in figure 2D), whereas opercular activity vanished. Similarly, in Patient D, BOLD signal increase in correlation with objectively detected lid spasms was observed in the left putamen (see figure 1D) and not in the opercula.

The putamen focus in session 2 of Patient B was weak compared with session 1 because quality of the fMRI data and significance levels were reduced as a result of the presence of the infrared eye position detector. However, the activation was significant when corrected for an ROI containing only the thalamus and basal ganglia (see table 2). This finding remains to be confirmed when other fMRI-compatible techniques objectively measuring eye blinks become available.

The BOLD signal time courses are illustrated for the putamen activation of both measurements of Patients A (see figure 2, A and B) and B (see figure 2, C and D). They indicate that neuronal activity in the putamen increased when the patients (see figure 2, A through C) or the infrared detector system (see figure 2D) reported the onset of a phase of lid spasms. The signal usually remained at a high level during the spasm episode and returned to a lower level after spasms stopped.

To estimate the influence of head movement related to eye blinks on patient data, we extracted the distance and time courses of the 3D motion correction in the three translation and rotation axes and correlated them with the reference functions or the ROI activations. First, head movements were not consistently correlated with spasm epochs (reference function; mean of the correlation coefficients = 0.071 ± 1) and were smaller than voxel size in all axes (<1 mm). Second, with a partial correlation analysis we could not detect any significant effect of movement on putamen ROI signal time courses. Correlation coefficients of putamen activations were changed in the range of 0.027 ± 0.019 when the highest correlated motion correction time course was excluded by

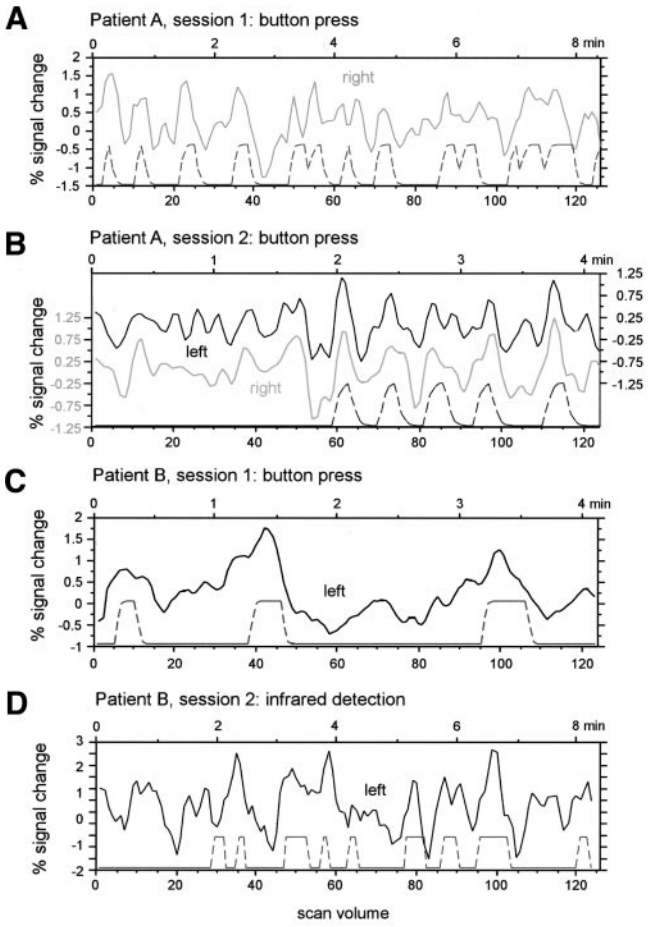

Figure 2. Filtered time courses of the average putamen blood oxygenation level-dependent (BOLD) signal from figure 1, A and B. The dashed black lines indicate the respective model functions as constructed from the button-press reference (A through C) and the infrared detection (D). Gray solid lines indicate right putamen time courses, and black solid lines indicate left putamen activations. (A, B) Putamen time courses in Patient A during the first measurement (A) and during the retest session 2 years later (B). (B) Note that the time courses of right and left putamen are similar. (C, D) Putamen time courses in Patient B during button press (C) and infrared detection (D).

partial correlation and significance levels did not change. Thus, we are assured that patient motion did not bias the data.

Discussion. In all six patients, unilateral or bilateral activation of the putamen correlated with eyelid spasm. These activations were reproducible after 2 years (Patient A) and with the infrared reference (Patient B). Putamen activation was not observed during voluntary blinking in any of the control subjects.

Most of the concomitantly activated areas in our study were not observed in all patients and can be related to either button press or voluntary eye blinks and associated motor preparation. In Patients C, E, and F, the primary sensorimotor cortex (PSMC) was activated contralaterally to the hand used for button presses. To optimize subcortical resolution, PSMC slices were not investigated in Patients A and B. Here, and in control subjects, frontal and parietal opercula were activated. Opercular activation has been described in somatosensory processing before[21,22] and did not occur during infrared detection in patients. Therefore, it is most likely to be related to button pressing or voluntary blinking. Primary and associative visual cortical areas were activated in patients and control subjects and have been previously reported during voluntary eye blinking.[23,24] This may reflect differences in retinal activation during frequent eye blinks as opposed to relaxed fixation. We found cerebellar activation in some patients, which is consistent with the PET finding of hypermetabolism in the cerebellum and pons of patients with blepharospasm during wakefulness.[14] However, because we and others[24] observed cerebellar activation also during voluntary blinking, it is probably not specific for BEB.

The size and exact location of the activated region in the putamen varied between patients and between measurements of the same patient (Patients A and B). However, Talairach coordinates confirmed foci of putamen activation in all patients (see table 2). Interindividual and intraindividual differences may result from the limited spatial resolution of fMRI. They could also potentially be caused by differences in noise level between patients and sessions induced by the eye tracking system. Artifactual putamen activation induced by head movements can be excluded because the influence of motion on the putamen time courses was negligible. Eye movement artifacts occasionally observed in frontal cortical areas should not have interfered with subcortical activation patterns because of the distance.

The putamen activation in our patients does not seem to be related to the button-pressing task, which agrees with previous fMRI studies showing that the putamen is not involved in simple finger movements.[25,26] First, there was no putamen activation in control subjects pressing a button. Second, putamen activation was observed during infrared detection sessions in patients (Patients B and D). Third, similar sites were activated in Patient B during button press and infrared detection. Furthermore, the side of putamen activation was not consistently related to the hand used for button pressing. Voluntary eye blinks and countermovements may accompany involuntary spasms. Confirming previous neuroimaging studies,[23,24,27] we did not observe any striatal activation with voluntary eyelid movements of control subjects. Putamen activation has so far only been implicated in reflex eye blinks to air puffs.[28]

FMRI lacks the temporal resolution to determine whether the striatal activation preceded or followed the onset of the eyelid spasm. Theoretically, the BOLD signal increases in the putamen could be correlates of a sensory feedback activation of this structure through the cortex rather than related to the motor output. However, the connectivity of the putamen,[29] the evidence from basal ganglia lesions, and

the lack of putamen activation during voluntary blinking lead us to assume that striatal activation in the present data is not purely sensory. This interpretation is further supported by reports from a recent [^{18}F]-deoxyglucose (FDG)–PET study of striatal and thalamic hyperactivity in patients with BEB, which indicates a pathologically enhanced glucose metabolism reflecting either increased excitatory or inhibitory neuronal activity in these regions.[12] Periodic hyperactivity of the striatum would be compatible with previously described D_2-receptor deficiency in these areas for patients with BEB and other focal dystonias.[11] This D_2-receptor abnormality was proposed to affect basal ganglia output to cortical premotor and motor areas through increased inhibition in the indirect inhibitory pathway from the putamen to the thalamus and, thus, decreased excitation in thalamocortical connections.[11] Indeed, another FDG–PET investigation comparing BEB patients with healthy subjects found hypoactivity in cortical areas controlling the eyelids during sleep.[14] Our observation of putaminal activation during eyelid spasms also points to a central role of the striatum in the pathophysiology of BEB. Whether the striatum is the site of the causal lesion or whether cortical areas delivering input to the basal ganglia are originally affected cannot be decided based on our data. Provided the necessary technical developments, future experiments with EMG during fMRI could lead to better model functions and determine the role and activation sequence of cortical and other subcortical areas beyond the putamen in the network underlying BEB.

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