Bilateral Functional MRI Activation of the Basal Ganglia and Middle Temporal/Medial Superior Temporal Motion-Sensitive Areas

Optokinetic Stimulation in Homonymous Hemianopia

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Objective: To determine to what extent sensorimotor control is achieved for each hemisphere separately or interactively during small-field optokinetic stimulation in patients with complete homonymous hemianopia.

Design: Functional and structural neuroimaging using high-resolution magnetic resonance imaging.

Setting: University medical center research facility.

Patients: Three patients with complete homonymous hemianopia after acute infarction of the right posterior cerebral artery.

Main Outcome Measures: Anatomical location of activated structures during horizontal optokinetic stimulation and T2-weighted anatomical magnetic resonance imaging.

Results: Occipitotemporal cortical areas (Brodmann areas 39 and 40) were the only activated cortical structures that showed statistically significant (P<.01) activation on the affected hemisphere. Of the subcortical areas, activation of thalamic nuclei appeared to be missing on the affected side, whereas the basal ganglia (putamen, globus pallidus, and caudate nucleus) were bilaterally activated.

Conclusions: Bilateral activation of the basal ganglia confirms the concept of the basal ganglia–thalamocortical motor loop and of the efference copy of oculomotor pathways from each hemisphere. Our findings suggest 2 possible explanations for the activation of occipitotemporal areas (the human homolog of middle temporal/medial superior temporal areas) on the infarcted hemisphere: involvement of direct extrastriatal visual pathways or interhemispheric callosal connections between right and left middle temporal/medial superior temporal areas.

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ULL-FIELD optokinetic stimulation activates both striate visual cortices, the motion-sensitive middle temporal/medial superior temporal areas (MT/MST), and multiple cortical oculomotor areas, such as the parietal eye field, the frontal eye field, the prefrontal cortex, and the supplementary eye field.1 Furthermore, the anterior and posterior insulae and the paramedian thalamus are activated. Efferent oculomotor activity can be traced by bilateral activation of the caudate nucleus, the putamen, and the globus pallidus. This pattern of activated areas reflects the sensorimotor processes that mediate perception of visual motion and optokinetic nystagmus. The temporal sequence of activation and the pathways by which the visual input is conveyed to other sensory (vestibular) or oculomotor areas are largely unknown.

To determine to what extent sensorimotor control is achieved for each hemisphere separately or interactively, we examined patients with acute complete homonymous hemianopia using functional magnetic resonance imaging (MRI) scans during small-field optokinetic stimulation.

RESULTS

High-resolution proton density and T2-weighted anatomical MRI scans showed infarction of the entire occipital territory of the posterior cerebral artery in all patients. In 1 patient the lesion extended to the parietal cortex as well. There were no additional structural abnormalities, in particular, no infarction of the temporal lobe or the thalamus in 2 of the 3 patients. Cerebral activation due to horizontal optokinetic stimulation was present in all patients. Repeated measurements of selected slices of the same patient showed consistent activation patterns regarding the extent and anatomical location. We de-
PATIENTS AND METHODS

PATIENTS

Three right-handed patients (aged 63, 75, and 76 years; 2 men and 1 woman, respectively) were examined 5 or 7 days after acute infarction of the right posterior cerebral artery using a 1.5-T standard clinical scanner (Siemens Vision, Erlangen, Germany). Visual field testing exhibited complete homonymous hemianopia in all patients, including the fovea for kinetic and stationary testing on the Goldmann perimeter. According to the institutional guidelines, all patients gave their informed written consent before undergoing the MRI scans.

MAGNETIC RESONANCE IMAGING

All experiments were performed on a 1.5-T scanner (Siemens Vision) using a circularly polarized head coil and a map shim for high homogeneity of the magnetic field. The patient’s head was positioned and fixed in the head coil in all 3 dimensions to minimize movement artifacts. High-resolution anatomical coronal and transversal proton density and T2-weighted images (repetition time, 5400 milliseconds; echo time proton density, 14 milliseconds; echo time T1, 99 milliseconds; = 5400/14/99 milliseconds; 352 × 512 matrix; 200-mm field of view; 3-mm slice thickness) were acquired for structural MRI scans to allow for later anatomical correlation with the stimulation data. Single-slice flow-sensitized images (repetition time, 75 milliseconds; echo time, 8 milliseconds; flip angle, 60°) delineated macrovasculature in these slices to exclude large vessels as a source of activation.

Functional images were acquired from 5 to 10 oblique transversal slices covering the cortex, the basal ganglia, and the thalamus with the same orientation of the anatomical images using a radiofrequency-spoiled fast low-angle shot pulse sequence with first-order motion compensation (repetition time, 63 milliseconds; echo time, 30 milliseconds; voxel size, 0.78 × 0.78 × 4 mm; bandwidth, 32 Hz/pixel), which has a high sensitivity to the inhomogeneous-weighted transverse relaxation time T2.3,4 Weak radiofrequency excitation pulses (flip angle, 10°) were applied for functional imaging to minimize potential in-flow contributions in macroscopic vessels as a direct source of functional MRI signal intensity changes.3 Shimming was performed for each location prior to acquisition to minimize system inhomogeneities and thus artificial image-to-image signal fluctuations.2

RECORDING PROCEDURE

Patients lay supine wearing prism glasses that allowed visual stimulation from outside the scanner. A rotating drum (diameter, 0.4 m; rotation velocity, 6°-8°/s) covered with colored objects was placed in front of the MRI scanner bore to elicit horizontal optokinetic nystagmus. Patients were instructed to fixate on the drum throughout the whole functional MRI acquisition without voluntarily moving their eyes. In the 3 patients tested under these conditions, slow-phase velocity was 6° to 8°/s; this was induced using slow-velocity drum rotation for both horizontal stimulation directions. Thus, the induced low-velocity nystagmus was symmetrical for rightward and leftward stimulation. Patients were scanned separately during viewing of the stationary optokinetic pattern with a fixation point, during horizontal rotation of the drum to the right, and during horizontal rotation of the drum to the left. Thirty-two serial images were continuously acquired at the same slice for drum rotation to the right and to the left separately over 7 minutes. Eight initial images at rest (with fixation) were followed by 8 images during drum rotation, followed again by a period of rest and rotation, resulting in a total of 32 serial images. The stimulated field subtended 20° in the horizontal and 15° in the vertical directions. Additionally, we studied 1 patient while optokinetically stimulating only the nonaffected right visual half-field in comparison with optokinetic stimulation of the full visual field. The different paradigms were chosen in a random manner. There was a rest period of 1 minute between each experimental run. Measurements of selected slices were repeated 3 times in each subject to ensure individual reproducibility.

An electro-oculogram, described in detail in a previous study,1 recorded the optokinetic nystagmus from both eyes during functional MRI acquisition with silver/silver chloride electrodes placed at the external canthi to monitor task performance and to exclude the possibility that voluntary saccades occurred while viewing both the stationary and the moving optokinetic pattern. A typical electro-oculogram recording during rest and the drum rotation conditions inside the MRI scanner is demonstrated in Figure 1.

IMAGE ANALYSIS

Functional activation maps were created on a pixel-by-pixel basis by correlating the time courses of the signal intensities with a periodic reference function comprising the stimulus protocol.4 Previous observations about functional MRIs suggested a stimulus-dependent rise latency of 6 to 12 seconds from baseline signal to signal cessation.2,5 To resemble the signal changes over time, the reference function thus chosen was a boxcar waveform consisting of 32 data points, shifted by 1 image to account for the hemodynamic latencies and rise times. Pixels that had values greater than 0.8 of the volume mean in all the images were selected to restrict the analysis to intracranial regions. Image analysis was performed off-line on a microcomputer using our own specially developed software as described in detail elsewhere.4 The analysis assigned a correlation coefficient (r) ranging from −1.0 to 1.0 to each pixel and generated a correlation coefficient image. Only those pixels with r ≥ 0.5 were analyzed further. This cutoff for a 32-image series corresponds to a statistical significance of P ≤ 0.005.4 To ensure that there were no areas less activated than the chosen statistically significant threshold of r ≥ 0.5, we also calculated correlation maps with a threshold of r ≥ 0.25. Red-yellow color-coded quantitative maps were superimposed onto the corresponding first anatomical image of the functional data set to enhance visualization and to localize activation in relation to cerebral anatomy.

As described in previous studies,1,7 the evaluation of our functional data refers to the anatomical location and the extent of activation (number of activated voxels). To test whether the activation condition is a significant factor, the number of activated voxels of all regions of interest were subjected to a repeated measures of analysis of variance with the stimulus task as the confounding variable. The extent of activated areas was then compared between right and left rotation of the drum using the Student t test after checking for normal distribution. The post hoc tests were used with a significant threshold set at a Bonferroni-adjusted α level of P < .01 following a correction for multiple nonindependent comparisons (equivalent to P < .001).
were bilaterally activated (Figure 2). On the Talairach including the putamen, globus pallidus, and caudate nucleus reaching a smaller threshold for the correlation coefficient of the infarcted hemisphere (Figure 2) even when applying a correlation coefficient scale ranges from 0.5 (red) to a maximum of 1.0 (yellow). Although the patient had complete homonymous hemianopia, we found bilateral activation of the lateral occipitotemporal cortex (O) (C-H [white arrows]). All other cortical areas including the parietal cortex (PF) (A and B), the precentral and posterior median frontal gyri (frontal eye fields [F]; A and B), parts of the parietal cortex including the parietal eye field (P) (A-H), the anterior part (AD) (G-I) and posterior part (PI) (G-J) of the insula, and the visual cortex (VC) (I and J) were not activated on the infarcted hemisphere. Thalamic and geniculate nucleus activity (T) (I and J) was not seen in the infarcted hemisphere, while other subcortical areas, such as the putamen (PU) (I and J), globus pallidus (GP) (I and J), and caudate nucleus (NC) (G and H) showed bilateral activation. Note that there is no difference in the anatomical location and extent of activation for both directions of object motion.

**Figure 1.** Electro-oculographic direct current recording from both eyes of a patient with complete homonymous hemianopia during fixation of the stationary optokinetic nystagmus (OKN) pattern and during horizontal OKN stimulation to the right while magnetic resonance imaging scans were performed. Arrows indicate beginning and end of the OKN stimulation period (57 seconds). Note the 16-Hz noise due to the radiofrequency pulse that corresponds to the repetition frequency of the excitation pulse (16 Hz) during magnetic resonance imaging.

T2-weighted coronal magnetic resonance imaging scans of 5 cortical sections of a 63-year-old patient with infarction of the right posterior cerebral artery that caused complete hemianopia. The superimposed activation maps are associated with optokinetic nystagmus induced by right (A, C, E, G, and I) and left (B, D, F, H, and J) motion stimulation. The color-coded correlation coefficient scale ranges from 0.5 (red) to a maximum of 1.0 (yellow). Although the patient had complete homonymous hemianopia, we found bilateral activation of the lateral occipitotemporal cortex (O) (C-H [white arrows]). All other cortical areas including the parietal cortex (PF) (A and B), the precentral and posterior median frontal gyri (frontal eye fields [F]; A and B), parts of the parietal cortex including the parietal eye field (P) (A-H), the anterior part (AD) (G-I) and posterior part (PI) (G-J) of the insula, and the visual cortex (VC) (I and J) were not activated on the infarcted hemisphere. Thalamic and geniculate nucleus activity (T) (I and J) was not seen in the infarcted hemisphere, while other subcortical areas, such as the putamen (PU) (I and J), globus pallidus (GP) (I and J), and caudate nucleus (NC) (G and H) showed bilateral activation. Note that there is no difference in the anatomical location and extent of activation for both directions of object motion.

**Figure 2.** T2-weighted coronal magnetic resonance imaging scans of 5 cortical sections of a 63-year-old patient with infarction of the right posterior cerebral artery that caused complete hemianopia. The superimposed activation maps are associated with optokinetic nystagmus induced by right (A, C, E, G, and I) and left (B, D, F, H, and J) motion stimulation. The color-coded correlation coefficient scale ranges from 0.5 (red) to a maximum of 1.0 (yellow). Although the patient had complete homonymous hemianopia, we found bilateral activation of the lateral occipitotemporal cortex (O) (C-H [white arrows]). All other cortical areas including the parietal cortex (PF) (A and B), the precentral and posterior median frontal gyri (frontal eye fields [F]; A and B), parts of the parietal cortex including the parietal eye field (P) (A-H), the anterior part (AD) (G-I) and posterior part (PI) (G-J) of the insula, and the visual cortex (VC) (I and J) were not activated on the infarcted hemisphere. Thalamic and geniculate nucleus activity (T) (I and J) was not seen in the infarcted hemisphere, while other subcortical areas, such as the putamen (PU) (I and J), globus pallidus (GP) (I and J), and caudate nucleus (NC) (G and H) showed bilateral activation. Note that there is no difference in the anatomical location and extent of activation for both directions of object motion.

Horizontal optokinetick nystagmus was associated with activity contralateral to the lesion site in the precentral and posterior median frontal gyri (Brodmann areas 8 and 9), in the prefrontal cortex (Brodmann area 46), in the area of the posterior parietal cortex (Brodmann areas 39 and 40), and in the visual cortex (Figure 2). Insular activation was found in 2 spatially separate areas using the Talairach 3-dimensional proportional grid system for referential orientation8 (Figure 2): in the anterior part (C-c-10 to D-c-11) and in the posterior part (E-c-10 to E-c-11) of the insula. Although all patients presented with complete homonymous hemianopia of the left visual field due to infarction of the right posterior cerebral artery, we found bilateral activation of the lateral occipitotemporal cortex (supplied by the middle cerebral artery) (Figures 2 and 3). This was the only cortical area of the infarcted right hemisphere in all patients that reached a statistically significant activation. There was no significant activation of the prefrontal cortex, the precentral and posterior median frontal gyri, the posterior parietal cortex, or the anterior and posterior insula on the infarcted hemisphere (Figure 2) even when applying a smaller threshold for the correlation coefficient of $r \geq 0.25$. In contrast, subcortical oculomotor pathways including the putamen, globus pallidus, and caudate nucleus were bilaterally activated (Figure 2). On the Talairach 3-dimensional proportional grid system,8 the anatomical location of caudate nuclei activation was D-a-8 to D-a-9. The thalami and the lateral geniculate body nuclei showed no significant activation on the affected side (Figure 2). The anatomical localization of the thalamic activation pattern ranged from E2-a-9 to E3-a-9 and from E3-a-7 to F-b-7.8 The most prominent response (largest extent of activation) was found in the primary visual cortex (mean $\pm SD$, 108.5 $\pm$ 10.1 voxels) and in the posterior parietal cortex (mean $\pm SD$, 112.4 $\pm$ 12.7 voxels).

Half-field stimulation of the nonaffected right visual field demonstrated a comparable activation pattern. Of the cortical pathways, only the lateral occipitotemporal cortices were activated on the affected right hemisphere (Figure 3). As seen with full-field stimulation, stimulation of the right visual half field also resulted in bilateral activation of subcortical oculomotor structures (putamen, globus pallidus, and caudate nucleus).

In all patients, the number of activated voxels in the occipitotemporal region was smaller (53%) in the infarcted right hemisphere (mean $\pm SD$, 22.8 $\pm$ 5.3 voxels) than in the noninfarcted left hemisphere (mean $\pm SD$, 26.5 $\pm$ 4.7 voxels), regardless of whether the drum rotated to the right or to the left. Analysis of variance for repeated measurements revealed no significant difference in the number of all activated voxels ($P > .10$) between drum rotation to the right (mean $\pm SD$, 635.3 $\pm$ 34.1 voxels) and drum rotation to the left (mean $\pm SD$, 612.4 $\pm$ 36.7 voxels). In addition, individual comparison of each activated area showed no significant difference ($P > .10$) in the extent of activation between both directions of drum rotation.

**COMMENT**

Cortical and subcortical activations during optokinetic stimulation can be related to the visual system, the oculomotor system, and visual-vestibular interaction.1,9-16 Comparison of activation patterns in both hemispheres revealed the following.

The precentral and posterior median frontal gyri, where the frontal eye field is located, the posterior parietal cortex that can be attributed to the parietal eye field, and the prefrontal cortex were activated only on the noninfarcted...
left hemisphere in all patients. In 1 patient the lesion extended to the parietal cortex and affected the parietal eye field. Each of these interconnected cortical areas has been implicated in oculomotor mechanisms on the basis of single-cell recordings in awake monkeys\(^\text{17,18}\) and in positron emission tomographic studies\(^\text{16,19}\) of humans.

Structures in the basal ganglia appear to be bilaterally activated despite the unilateral striatal visual input. Our data confirm the concept of a basal ganglia–thalamocortical motor loop (frontal eye field, caudate nucleus, globus pallidus, and thalamus), which Alexander et al\(^\text{20}\) proposed as the “oculomotor circuit” in primates. Earlier primate studies favor a role of the basal ganglia in the control of movement direction and the scaling of movement amplitude and velocity.\(^\text{20,21}\) Moreover, bilateral activation may reflect a bilateral downstream efference\(^\text{20}\) of oculomotor pathways from each hemisphere (frontal and parietal eye fields, and prefrontal cortex) via the superior colliculi to the pontine oculomotor nuclei.\(^\text{22}\) It is unlikely that the activation of the basal ganglia in our study is due to nonoculomotor activity, since the activation pattern reflects the difference between the 2 otherwise identical conditions of presenting a moving vs a stationary pattern. Bilateral basal ganglia activation corresponds to the clinical experience that most cortical oculomotor deficits in acute unilateral hemispheric lesions are transient. However, our findings do not allow us to identify the pathways by which the basal ganglia are activated on the affected side: bilateral projections to right and left basal ganglia from each hemisphere (eg, originating in the frontal eye field), bilateral thalamic projections from the noninfarcted hemisphere, ipsilateral projections from the occipitotemporal cortex of each hemisphere, or direct interconnections between right and left basal ganglia are all possible.

Anterior and posterior insulae (the posterior insula as the human homolog of the parietoinsular vestibular cortex\(^\text{23}\)) also showed activation only on the noninfarcted hemisphere and therefore rely on the visual input from the ipsilateral hemisphere. The same holds for the thalamus, which in part (pulvinar) can be considered to project to the inner circle of the vestibular cortex.\(^\text{24}\)

Activation of occipitotemporal areas corresponds best with the human homolog of MT/MST. These areas provide us with intermediate information about visual motion in extraretinal coordinates, which can be used for motor control of not only the eyes but also the body. Bilateral MT/MST activation may be based on direct ipsilateral or contralateral transcallosal visual input. Interthalamic connections between occipitotemporal areas MT/MST (V5) have been described in monkeys.\(^\text{25}\) Ipsilateral visual information can bypass V1 along several pathways, among them the superior colliculus–pulvinar route and the lateral geniculate body nucleus route to the prestriate cortex as described in monkeys.\(^\text{26,27}\) The lateral and inferior pulvinar of the thalamus and the lateral geniculate body nucleus were not significantly activated on the infarcted side in our patients.

Ipsilateral pathways directly from the geniculate bodies not affected by posterior cerebral artery infarctions may provide MT/MST with visual motion information independent of the stimulation of areas V1 to V3. In fact, an earlier study described 2 patients who had almost complete destruction of the striate cortex but could con-

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**Figure 3.** Magnified functional magnetic resonance imaging scans of a 75-year-old patient with infarction of the right posterior cerebral artery. Activation maps associated with optokinetic stimulation of the full field (A and C) and of the nonaffected right visual half field (B and D) are shown. Both kinds of stimulation led to a comparable activation pattern in the parietal cortex including the parietal eye field (P) (A–D). Of the cortical pathways, only the lateral occipitotemporal cortex (O) was activated on the affected right hemisphere (A–D, white arrows), both during full-field and half-field stimulation.
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