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# Eye closure in darkness animates sensory systems

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**Abstract**

Single subject and group analyses ($n = 12$) showed that the eyes-open and eyes-closed states in complete darkness considerably and consistently differ in the patterns of associated brain activation in fMRI. During nonchanging external stimulation, ocular motor and attentional systems were activated when the eyes were open; the visual, somatosensory, vestibular, and auditory systems were activated when the eyes were closed. These data suggest that there are two different states of mental activity: with the eyes closed, an "interoceptive" state characterized by imagination and multisensory activity and with the eyes open, an "exteroceptive" state characterized by attention and ocular motor activity. Our study also shows that the chosen baseline condition may have a considerable impact on activation patterns and on the interpretation of brain activation studies.


## Introduction

The identification of a baseline or control state is fundamental for the interpretation of brain activation studies (Gusnard and Raichle, 2001). Raichle et al. (2001) suggested the existence of an organized default mode of brain function that is suspended during goal-directed behavior. This view was supported in a metaanalysis of PET studies comparing goal-directed tasks to rest conditions with eyes closed (Mazoyer et al., 2001). Eyes-open and eyes-closed conditions in complete darkness serve as rest conditions in human brain imaging studies. However, they could have nontrivial differential effects on brain activity. Theoretically, the eyes-open and eyes-closed states may induce modulations in visual, ocular motor, or attentional structures despite the lack of any associated changes in external sensory stimulation. Two opposite modulations of brain activity are conceivable. First, eyes open in darkness may elicit a status of higher alertness with readiness and expectation to see, which could be associated with higher activity in visual and ocular motor systems. Second, eye closure could initiate activations of cortical visual and ocular motor structures, e.g., by the imagination of visual scenes. Furthermore, ocular motor activity may differ during the two conditions and thus account for modulations in brain activity. We conducted an fMRI study ($n = 12$) in healthy volunteers to compare eyes-open vs eyes-closed conditions in darkness. Eye movements were recorded for the same conditions outside the scanner. In order to identify the pattern of brain activation typical for the two conditions, statistical parametric maps were computed to compare the mean blood oxygenation level-dependent (BOLD) signal differences.

## Methods

### *MRI experiment*

#### *Subjects*

Twelve healthy volunteers (eight females, four males; ages 20–38 years; mean age 26.3 years) participated; two were examined a second time 6-months later to test for

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intraindividual reliability. All subjects gave their informed written consent.

*Experimental procedure*

Subjects lying in the MRI scanner in complete darkness with the head carefully fixed in place were instructed to alternately open and close their eyes for periods of 22.5 s in response to an acoustic signal given via earphones. The experiment began for all subjects with the eyes-closed condition, followed by 11 blocks in which the eyes-open and eyes-closed conditions alternated. The acoustic signal consisted of the monosyllabic words "auf" or "zu" (German for "open" or "close"). Subjects were asked to keep their eyes straight ahead and still and no fixation target was presented. Subjects were instructed to relax and not to move. No instructions were given as to mental activity and subjects were not debriefed after the scanning.

*Data acquisition*

Functional images were acquired on a 1.5 T standard clinical scanner (Siemens Vision, Erlangen, Germany) using echo-planar imaging (EPI) with a T2*-weighted gradient-echo multislice sequence (TE = 60 ms, voxel size 3.75 × 3.75 × 3.75 $mm^3$, matrix 64 × 64, interscan interval 4.5 s). Thirty-two transversal slices covered the whole brain and upper parts of the cerebellum. Each scanning session comprised two successive series consisting of 120 images each with alternating eyes-open and eyes-closed conditions.

*Data analysis*

Data processing was performed on UltraSPARC workstations (Sun Microsystems) using statistical parametric mapping (SPM99) (Friston et al., 1995b) implemented in MATLAB (Mathworks, Sherborn, MA, USA). The first five images of each imaging run were discarded to eliminate spin saturation effects. Motion correction was performed by realigning every volume to the first one of each scanning session, using the method described by Friston et al. (1995a). In an earlier study we found that lid closure increased signal intensity of the eyes by a factor of 1.6 to 2 in EPI-fMRI (Stephan et al., 2002b). If the eyes were included in the scanning volume, the different states of eyes open and eyes closed in darkness were regularly associated with erroneously detected head translations along the $z$ axis and head rotations around the $x$ axis in Talairach's coordinate system. These artifacts were avoided by masking the eyes in the images while estimating movement parameters. The same procedure of masking the eyes was performed during head motion correction in the current study. After motion correction the image volumes were spatially normalized (Friston et al., 1995a) into the standard space defined by the Montreal Neurological Institute (MNI) template. After normalization, the image volumes had a voxel size of 2 × 2 × 2 $mm^3$. Following normalization, the area containing both eyes was manually masked and erased from the image volumes to avoid confounding of the global brain signal (Stephan et al., 2002b). Subsequently, the data sets were smoothed with a 12-mm (FWHM) isotropic Gaussian kernel to compensate for intersubject gyral variability and to attenuate high-frequency noise, thus increasing the signal-to-noise ratio. SPM99 estimated a resulting smoothness of 17.3 × 17.3 × 15.4 $mm^3$. Proportional scaling was applied to normalize global means. For the single-subject analyses, statistical parametric maps were calculated using the general linear model (Friston et al., 1995b) with a hemodynamic model of the two states of the experiment. To allow inference to the general population, fMRI group analysis was performed by collapsing repeated measures within subjects and experimental runs. The resulting 24 condition images (one image per condition per subject) were compared between subjects, thereby effecting a random effects model. Statistical parametric maps were calculated on a voxel-by-voxel basis using the general linear model (Friston et al., 1995b) and the theory of Gaussian fields (Worsley and Friston, 1995). For single subject and group analyses, results exceeding a height threshold of $P \leq 0.001$ and an extent threshold of three voxels was considered significant.

To define the anatomical sites of activation clusters, we used MNI coordinates and the parcellation method along with the automated anatomical labeling software described by Tzourio-Mazoyer et al. (2002). Cerebellar activation sites were named according to Schmahmann et al. (2000).

*Electronystagmography*

In a second experiment, horizontal and vertical eye movements were recorded by means of DC electronystagmography (ENG) (Toennies, Germany) outside the scanner for the eyes-open and eyes-closed conditions in complete darkness (six healthy volunteers, three females, three males; ages 26–38 years; mean age 28.5 years). Mean velocities of horizontal eye movements were computed and compared for both conditions. The vertical components were used for automatic detection and elimination of blink artifacts. The resolution of ENG is about 1°.

## Results

Task-related changes in fMRI signal intensities were seen in both the group analysis and all single-subject analyses ($P < 0.001$, uncorrected).

In the group analysis with the *eyes closed* (eyes closed > eyes open), activation clusters centered bilaterally in visual, somatosensory, vestibular, and auditory cortical areas, as well as in the medial frontal gyri (Fig. 1). The activation cluster in the visual cortex included the inferior, middle, and superior occipital gyri, the fusiform gyri, and the lingual gyri. It extended into the middle and inferior temporal gyri (Table 1), but spared the primary visual area (PVA/V1).

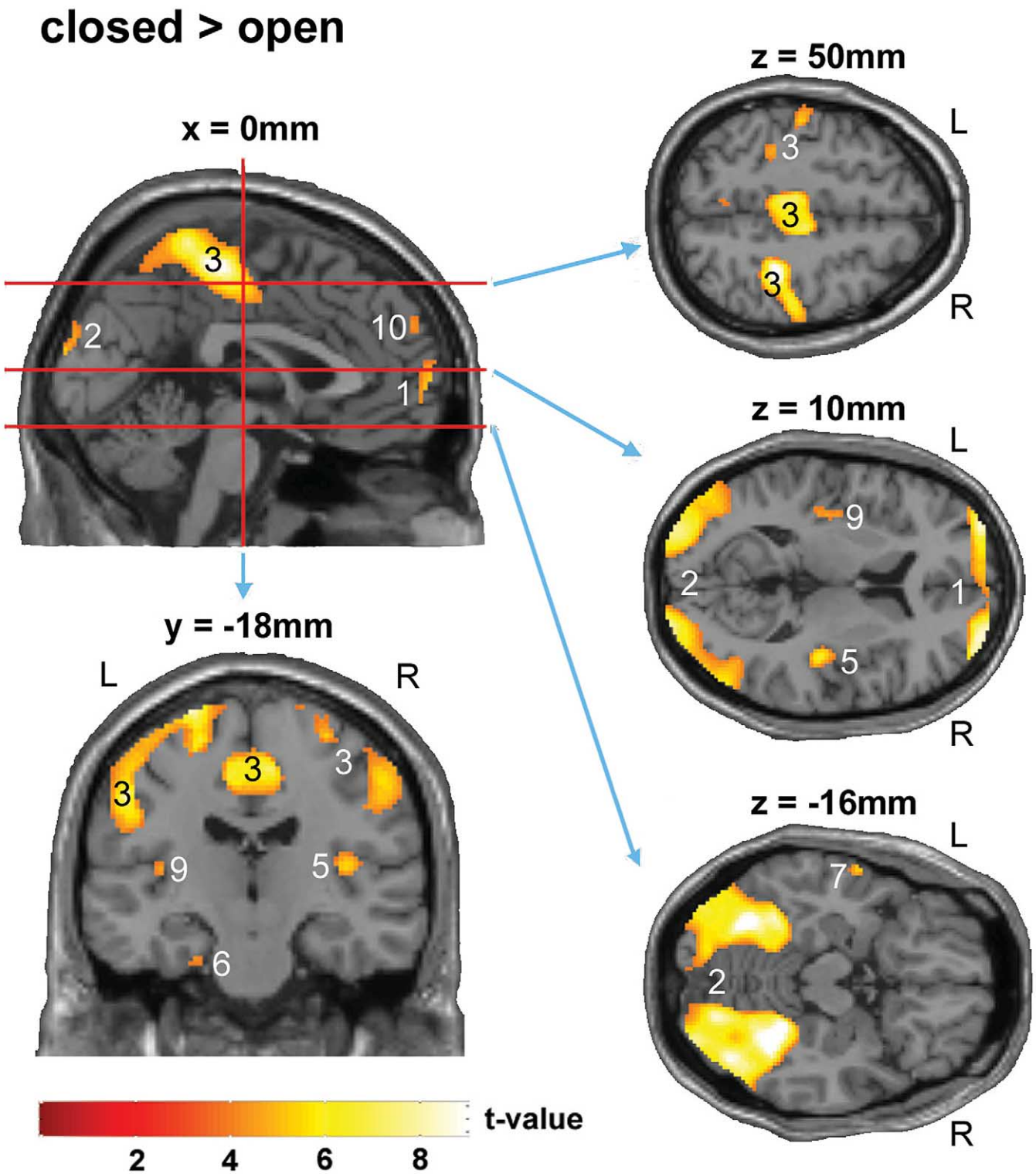


Fig. 1. BOLD-signal increases obtained by statistical group analysis for the comparison eyes closed minus eyes open in darkness. Activations are projected onto a standard template brain ($P < 0.001$, n = 12) for sagittal, coronal, and transverse sections (16 mm below, 10 and 50 mm above the anterior–posterior commissural line). Numbers indicate clusters according to Table 1, where anatomical attributions are listed. Activations involve visual (2), somatosensory (3), vestibular and auditory (5, 9), and frontopolar (1) areas bilaterally.

Activation of the somatosensory system was observed in the postcentral gyri, and activation of the vestibular system was located in posterior and retroinsular areas (parietoinsular vestibular cortex, PIVC). The latter cluster extended into the transverse temporal gyrus (Heschl's gyrus), which represents the auditory cortex.

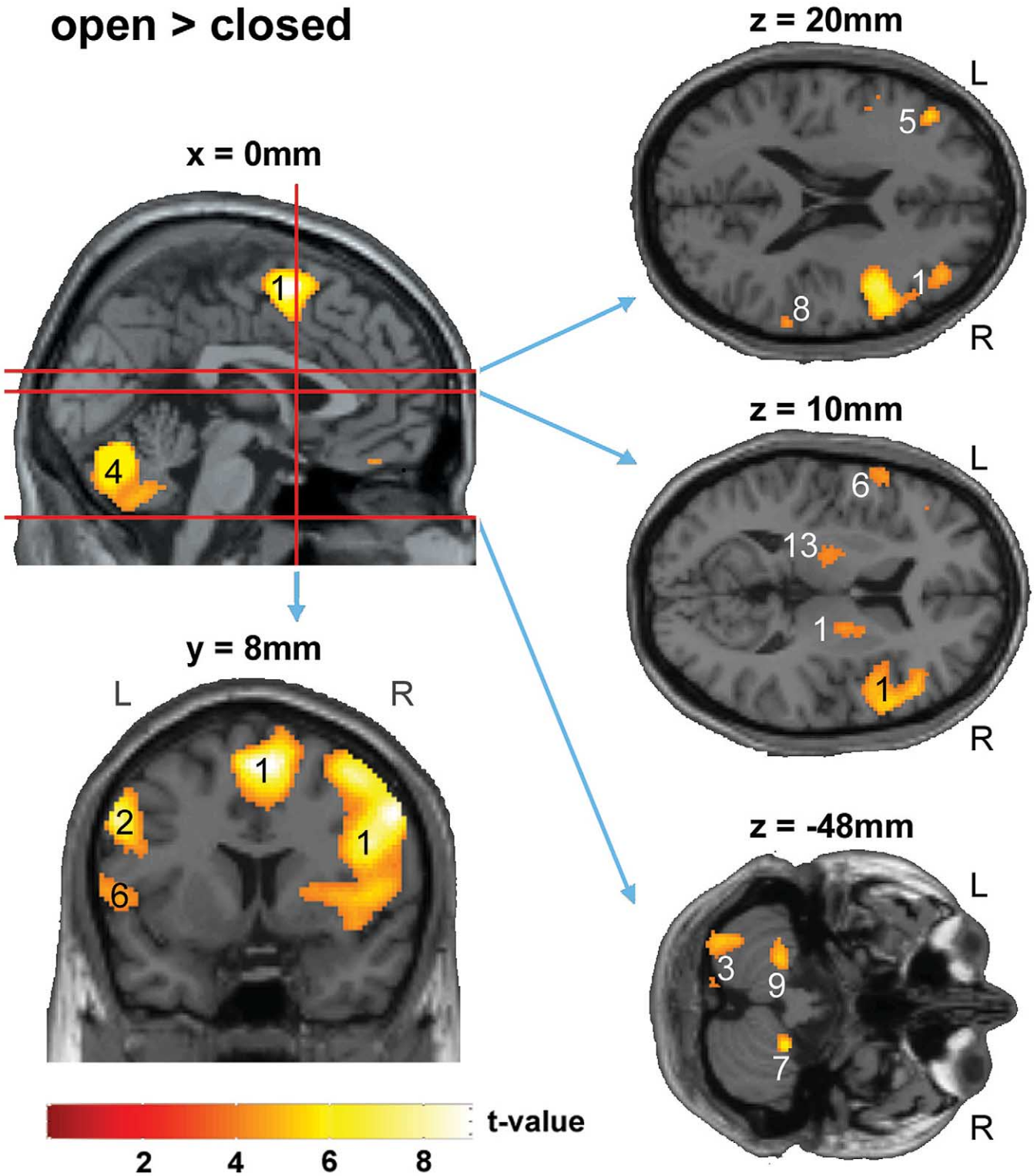


Fig. 2. BOLD-signal increases obtained by statistical group analysis for the comparison eyes open minus eyes closed in darkness. Activations are projected onto a standard template brain ($P < 0.001$, $n = 12$) for sagittal, coronal, and transverse sections (48 mm below, 10 and 20 mm above anterior–posterior commissural line). Numbers indicate clusters according to Table 2, where anatomical attributions are listed. Activations involve areas that correspond best to ocular motor structures such as DLPFC (1, 5), frontal (1, 2), supplementary (1), and parietal eye fields (10, not shown on selected slices), thalamus (1, 13), and the cerebellar vermis (4). Activations are also seen in the cerebellar hemispheres (3, 7, 9) and in the right hemisphere (1), including the prefrontal and precentral cortex. The latter structures are known to subserve attentional function.

Table 1
Activation areas for the contrast eyes-closed minus eyes-open

| Number | *x*, *y*, *z* [mm] | Label | % | k | T |
|---|---|---|---|---|---|
| **1** | | | | **2033** | |
| | **22 60 0** | **Frontal_Sup_R** | **17.22** | **350** | **20.49** |
| | | Frontal_Sup_L | 14.26 | 290 | |
| | | Frontal_Sup_Medial_L | 11.66 | 237 | |
| | | Frontal_Sup_Orb_R | 8.51 | 173 | |
| | | Frontal_Mid_Orb_R | 7.72 | 157 | |
| | | Frontal_Mid_L | 7.38 | 150 | |
| | | Frontal_Mid_R | 7.18 | 146 | |
| | −18 60 −2 | Frontal_Sup_Orb_L | 6.64 | 135 | 20.38 |
| | | Frontal_Sup_Medial_R | 6.39 | 130 | |
| | 32 62 −10 | Frontal_Mid_Orb_R | 4.72 | 96 | 19.23 |
| | | Frontal_Mid_Orb_L | 3.30 | 67 | |
| | | Frontal_Mid_Orb_L | 2.51 | 51 | |
| | | OOP | 2.51 | 51 | |
| **2** | | | | **13676** | |
| | | Occipital_Mid_L | 10.95 | 1498 | |
| | | Fusiform_R | 10.78 | 1474 | |
| | −32 −58 −8 | Fusiform_L | 10.04 | 1373 | 12.89 |
| | **−24 −80 −4** | **OOP (inferior occipital gyrus/lingual gyrus)** | **8.32** | **1138** | **13.28** |
| | | Lingual_R | 8.28 | 1132 | |
| | | Lingual_L | 6.52 | 892 | |
| | | Occipital_Inf_R | 6.24 | 853 | |
| | | Occipital_Inf_L | 5.94 | 812 | |
| | | Occipital_Mid_R | 5.11 | 699 | |
| | | Temporal_Inf_R | 4.42 | 604 | |
| | 30 −48 −20 | Cerebellum_6_R | 3.77 | 516 | 12.36 |
| | | Temporal_Mid_R | 3.25 | 444 | |
| | | Cerebellum_6_L | 2.51 | 343 | |
| | | Cerebellum_Crus1_R | 2.22 | 304 | |
| | | Occipital_Sup_R | 1.78 | 243 | |
| | | Cerebellum_Crus1_L | 1.44 | 197 | |
| | | Occipital_Sup_L | 1.38 | 189 | |
| | | Cerebellum_4_5_R | 1.37 | 187 | |
| | | Temporal_Mid_L | 1.05 | 144 | |
| **3** | | | | **8887** | |
| | 32 −30 52 | Postcentral_R | 24.76 | 2200 | 10.63 |
| | | Postcentral_L | 16.03 | 1425 | |
| | **−8 −40 70** | **Precuneus_L** | **10.16** | **903** | **11.82** |
| | | Paracentral_Lobule_L | 9.79 | 870 | |
| | −22 −22 76 | Precentral_R | 8.06 | 716 | 10.24 |
| | | Precentral_L | 6.22 | 553 | |
| | | Paracentral_Lobule_R | 4.93 | 438 | |
| | | OOP | 4.03 | 358 | |
| | | Cingulum_Mid_R | 3.04 | 270 | |
| | | Supp_Motor_Area_R | 2.67 | 237 | |
| | | Parietal_Sup_L | 2.66 | 236 | |
| | | Parietal_Sup_R | 2.12 | 188 | |
| | | Cingulum_Mid_L | 2.06 | 183 | |
| | | Precuneus_R | 1.17 | 104 | |
| | | Supp_Motor_Area_L | 1.14 | 101 | |
| **4** | | | | **23** | |
| | **−30 36 46** | **Frontal_Mid_L** | **86.96** | **20** | **6.74** |
| | | OOP | 13.04 | 3 | |
| **5** | | | | **160** | |
| | **42 −24 12** | **Heschl_R** | **43.75** | **70** | **6.56** |
| | | Insula_R | 21.88 | 35 | |
| | | Rolandic_Oper_R | 21.88 | 35 | |
| | | Temporal_Sup_R | 12.50 | 20 | |
| **6** | | | | **306** | |
| | −20 −8 −30 | ParaHippocampal_L | 46.41 | 142 | 6.29 |
| | | Fusiform_L | 21.57 | 66 | |
| | **−34 −4 −48** | **OOP (temporal pole)** | **17.97** | **55** | **6.50** |
| | | Temporal_Inf_L | 12.42 | 38 | |
| | | Temporal_Pole_Mid_L | 1.31 | 4 | |

Table 1 (*continued*)

| Number | *x*, *y*, *z* [mm] | Label | % | k | T |
|---|---|---|---|---|---|
| **7** | **−60 −4 −16** | **Temporal_Mid_L** | **100** | **22** | **5.26** |
| **8** | **24 −72 58** | **Parietal_Sup_R** | **100** | **4** | **4.66** |
| **9** | | | | **91** | |
| | **−36 −22 12** | **Insula_L** | **47.25** | **43** | **4.61** |
| | −38 −12 6 | Insula_L | | | 4.58 |
| | | Heschl_L | 23.08 | 21 | |
| | −48 −36 14 | Temporal_Sup_L | 15.38 | 14 | 4.40 |
| | | Rolandic_Oper_L | 14.29 | 13 | |
| **10** | | | | **89** | **4.31** |
| | **2 58 30** | **Frontal_Sup_Medial_L** | **60.67** | **54** | **4.31** |
| | −8 62 34 | Frontal_Sup_Medial_L | | | 4.24 |
| | 14 62 30 | Frontal_Sup_Medial_R | 30.34 | 27 | 4.15 |
| | | Frontal_Sup_R | 5.62 | 5 | |
| | | Frontal_Sup_L | 3.37 | 3 | |
| **11** | | | | **9** | |
| | **54 8 −26** | **Temporal_Pole_Mid_R** | **77.78** | **7** | **4.04** |
| | | Temporal_Mid_R | 22.22 | 2 | |

*Note.* Montreal Neurological Institute (MNI) coordinates, anatomical labels, and percentages are given according to Tzourio-Mazoyer et al., 2002. T = *t* value of local maximum, k = cluster size [voxels]; bold type indicates cluster maximum. Only clusters exceeding four voxels are shown; numbers of voxels for each anatomical region were computed and rounded to whole numbers. t Values and MNI coordinates are listed for three local maxima reaching the highest *t* values. (OOP, outside of parcellation.)

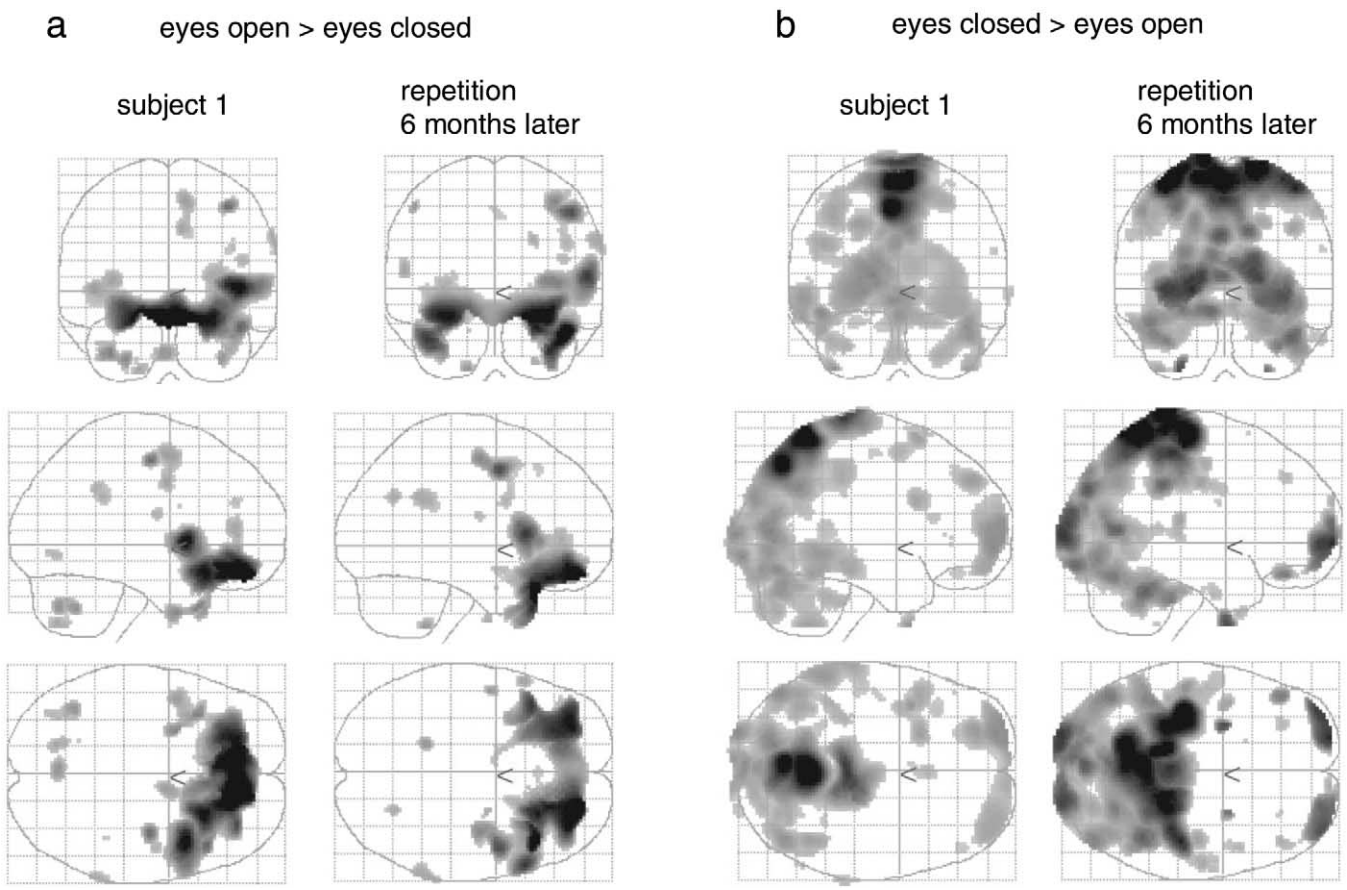


Fig. 3. Glass brain views for subject 1 who was measured twice within 6 months. Patterns of BOLD-responses in the eyes-open vs eyes-closed conditions correspond to those in the group analysis and exhibit a good intraindividual reproducibility ($P < 0.001$, $n = 1$).

Table 2
Activation areas for the contrast eyes-open minus eyes-closed

| Number | *x*, *y*, *z* [mm] | Label | % | k | T |
|---|---|---|---|---|---|
| **1** | | | | **12197** | |
| | | OOP | 12.10 | 1476 | |
| | | Frontal_Mid_R | 10.27 | 1253 | |
| | | Precentral_R | 9.36 | 1142 | |
| | | Frontal_Inf_Oper_R | 9.25 | 1128 | |
| | | Supp_Motor_Area_R | 7.86 | 959 | |
| | 36 38 −20 | Frontal_Inf_Orb_R | 6.95 | 848 | 11.67 |
| | | Frontal_Inf_Tri_R | 6.17 | 753 | |
| | | Insula_R | 6.08 | 742 | |
| | **−36 38 −18** | **Frontal_Inf_Orb_L** | **6.00** | **732** | **21.12** |
| | | Frontal_Sup_R | 4.01 | 489 | |
| | | Supp_Motor_Area_L | 3.16 | 385 | |
| | −24 34 −20 | Frontal_Mid_Orb_L | 2.03 | 248 | 13.56 |
| | | Frontal_Mid_Orb_R | 1.93 | 235 | |
| | | Frontal_Sup_Orb_R | 1.78 | 217 | |
| | | Temporal_Pole_Sup_R | 1.60 | 195 | |
| | | Rectus_L | 1.50 | 183 | |
| | | Rectus_R | 1.44 | 176 | |
| | | Putamen_R | 1.37 | 167 | |
| | | Frontal_Sup_Orb_L | 1.22 | 149 | |
| | | Insula_L | 1.21 | 148 | |
| **2** | | | | **900** | |
| | **−56 6 36** | **Precentral_L** | **77.78** | **700** | **7.86** |
| | −36 −10 50 | Precentral_L | | | 6.97 |
| | −48 0 48 | Precentral_L | | | 5.46 |
| | | Frontal_Mid_L | 9.33 | 84 | |
| | | Frontal_Inf_Oper_L | 8.44 | 76 | |
| | | Postcentral_L | 2.67 | 24 | |
| | | OOP | 1.56 | 14 | |
| **3** | | | | **632** | |
| | **−34 −84 −34** | **Cerebellum_Crus2_L** | **59.49** | **376** | **7.35** |
| | −36 −74 −50 | Cerebellum_Crus2_L | | | 5.11 |
| | | Cerebellum_Crus1_L | 27.53 | 174 | |
| | | OOP | 7.28 | 46 | |
| | | Cerebellum_7b_L | 5.06 | 32 | |
| **4** | | | | **1407** | |
| | −10 −84 −36 | Cerebellum_Crus2_L | 22.46 | 316 | 4.97 |
| | **6 −78 −20** | **Vermis_7** | **13.15** | **185** | **6.99** |
| | 0 −70 −22 | Vermis_6 | 10.66 | 150 | 6.60 |
| | | Vermis_8 | 9.81 | 138 | |
| | | Cerebellum_Crus2_R | 9.59 | 135 | |
| | | Cerebellum_6_L | 6.89 | 97 | |
| | | Cerebellum_Crus1_L | 6.89 | 97 | |
| | | OOP | 5.12 | 72 | |
| | | Cerebellum_Crus1_R | 4.41 | 62 | |
| | | Cerebellum_6_R | 3.48 | 49 | |
| | | Vermis_9 | 2.56 | 36 | |
| | | Cerebellum_7b_L | 1.85 | 26 | |
| | | Cerebellum_8_L | 1.63 | 23 | |
| | | Cerebellum_8_R | 1.14 | 16 | |
| **5** | | | | **95** | |
| | **−42 38 18** | **Frontal_Mid_L** | **53.68** | **51** | **6.88** |
| | | Frontal_Inf_Tri_L | 46.32 | 44 | |
| **6** | | | | **264** | |
| | | Frontal_Inf_Oper_L | 47.73 | 126 | |
| | | Rolandic_Oper_L | 17.42 | 46 | |
| | **−58 16 4** | **Frontal_Inf_Tri_L** | **17.42** | **46** | **6.75** |
| | | OOP | 10.61 | 28 | |
| | | Temporal_Pole_Sup_L | 6.82 | 18 | |
| **7** | | | | **59** | |
| | **24 −40 −50** | **Cerebellum_8_R** | **40.68** | **24** | **6.74** |
| | | Cerebellum_9_R | 37.29 | 22 | |
| | | Cerebellum_10_R | 18.64 | 11 | |
| | | OOP | 3.39 | 2 | |

Table 2 (*continued*)

| Number | *x*, *y*, *z* [mm] | Label | % | k | T |
|---|---|---|---|---|---|
| **8** | | | | **268** | |
| | **66 −32 26** | **SupraMarginal_R** | **88.43** | **237** | **5.40** |
| | 68 −30 38 | SupraMarginal_R | | | 4.42 |
| | | Temporal_Sup_R | 9.70 | 26 | |
| | | OOP | 1.87 | 5 | |
| **9** | | | | **138** | |
| | **−26 −44 −48** | **Cerebellum_8_L** | **78.26** | **108** | **5.25** |
| | −34 −42 −46 | Cerebellum_8_L | | | 4.75 |
| | | Cerebellum_9_L | 15.22 | 21 | |
| | | Cerebellum_Crus1_L | 3.62 | 5 | |
| | | Cerebellum_7b_L | 2.90 | 4 | |
| **10** | | | | **216** | |
| | **48 −52 54** | **Parietal_Inf_R** | **68.52** | **148** | **4.98** |
| | 42 −62 56 | Parietal_Inf_R | | | 4.63 |
| | | Angular_R | 27.31 | 59 | |
| | | OOP | 2.78 | 6 | |
| | | Parietal_Sup_R | 1.39 | 3 | |
| **11** | | | | **14** | |
| | **−24 −50 42** | **OOP (Precuneus/inferior parietal lobule)** | **78.57** | **11** | **4.74** |
| | | Parietal_Inf_L | 21.43 | 3 | |
| **12** | | | | **20** | |
| | **16 −94 −34** | **Cerebellum_Crus2_R** | **70.00** | **14** | **4.46** |
| | 24 −92 −38 | Cerebellum_Crus2_R | | | 4.10 |
| | | OOP | 30.00 | 6 | |
| **13** | | | | **81** | |
| | −18 −6 8 | OOP (Thalamus/Pallidum) | 51.85 | 42 | 4.10 |
| | **−18 −16 12** | **Thalamus_L** | **35.80** | **29** | **4.30** |
| | | Pallidum_L | 11.11 | 9 | |
| | | Putamen_L | 1.23 | 1 | |
| **14** | **40 −68 40** | **Angular_R** | **100.00** | **14** | **4.04** |
| **15** | **28 −20 −2** | **OOP (mesencephalon)** | **100.00** | **10** | **4.00** |
| **16** | | | | **5** | |
| | **−28 −24 −8** | **OOP (mesencephalon)** | **80.00** | **4** | **3.93** |
| | | Hippocampus_L | 20.00 | 1 | |
| **17** | **40 −58 42** | **Angular_R** | **100.00** | **5** | **3.92** |

*Note*. MNI coordinates, anatomical labels, and percentages are given according to Tzourio-Mazoyer et al., 2002, T = *t* value of local maximum, k = cluster size [voxels]; bold type indicates cluster maximum. Only clusters exceeding five voxels are shown; numbers of voxels for each anatomical region were computed and rounded to whole numbers. *t* Values and MNI coordinates are listed for the three local maxima reaching the highest *t* values. (OOP; outside of parcellation.)

In single-subject analyses, activations in the visual cortex were seen in 11 of 12 subjects, of the somatosensory cortex in eight, and of the vestibular and auditory cortices in four subjects. Repetitions of measurements in two subjects after 6 months revealed an intraindividually highly consistent pattern of BOLD-signal changes during

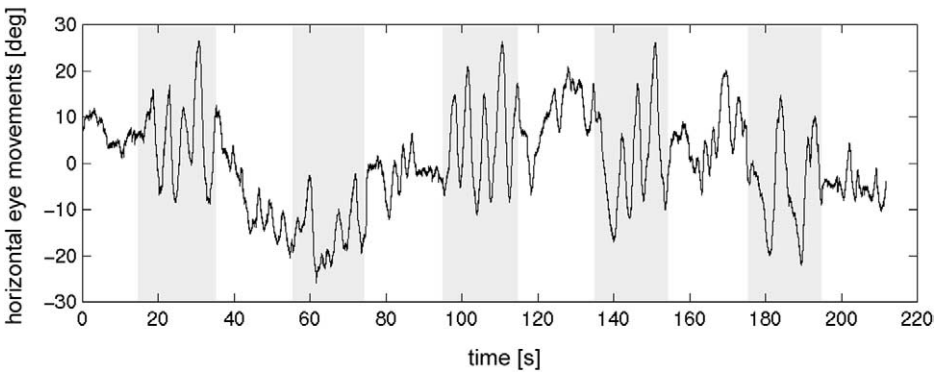


Fig. 4. Horizontal eye movements during the eyes-open and eyes-closed conditions in darkness. Original recording of DC-electronystagmography of one subject; shaded blocks correspond to eye closure phases. A different pattern of eye movements in the eyes-closed phases compared to eyes-open phases is revealed. Velocity and amplitude of eye movements (mainly involuntary pendular deviations) increase during eyes-closed phases.

the eyes-open and eyes-closed conditions in darkness (Fig. 3).

Group analysis with the *eyes open* (eyes open > eyes closed) showed that activation clusters centered in the cortical and subcortical ocular motor structures and in areas that can be best attributed to the attentional system (Fig. 2, Table 2). Ocular motor structures were represented by cerebellar activations in vermal lobules VI–IX, as well as in cerebellar hemispheres (left crus I + II; lobules VIII + IX bilaterally). There were also bilateral activations in the precentral gyri (including the frontal eye fields, FEF, and the supplementary motor area, SMA), extending into the middle and inferior frontal gyri (dosolateral prefrontal cortex, DLPFC). Basal ganglia activation occurred bilaterally in the striatum, extending into the thalamus. The attentional structures were represented by a large unilateral cluster in the right frontal lobe including the middle and inferior frontal gyri, extending into the temporal pole and the anterior insula, as well as by two smaller clusters in the right posterior inferior parietal lobule (Table 2).

In single-subject analyses, activations of ocular motor structures were seen in most subjects (vermis: $n = 11$; left cerebellar hemisphere: $n = 11$; right cerebellar hemisphere: $n = 7$; SMA: $n = 12$; left FEF: $n = 9$; striatum and thalamus: $n = 6$). Individual activations in attentional structures were found in all subjects (right prefrontal cortex: $n = 12$; inferior parietal lobule: $n = 8$). Again, repetitions of measurements in two subjects after 6 months revealed an intraindividually highly consistent pattern of BOLD-signal changes (Fig. 3).

*Eye movement recordings* showed mainly horizontal pendular deviations in both conditions (Fig. 4). Mean velocities were significantly higher ($P < 0.05$, $t$ test) with the eyes closed (10.12 ± 2.73 deg/s) than with the eyes open (7.69 ± 2.01 deg/s) in darkness (Fig. 5).

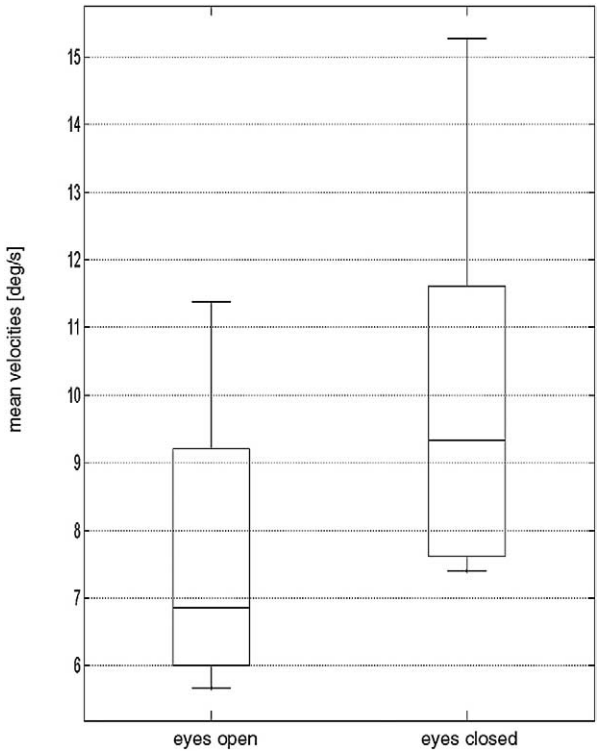


Fig. 5. Mean velocities of horizontal eye movements averaged across the group ($n = 6$) during eyes-open and eyes-closed conditions in darkness: box plot diagram showing the minimum, lower quartile, median, upper quartile, and maximum of the data. Mean velocities are significantly higher ($P < 0.05$) during the eyes-closed phases.

## Discussion

The two states of eyes open and eyes closed in darkness cause considerable and consistent changes in the patterns of brain activation. These alterations were evident in both single-subject and group analyses.

### *An "exteroceptive mental state" (eyes open > eyes closed)?*

The ocular motor and attentional systems seem to be predominantly activated when the eyes are open. Ocular motor activity is reflected by signal increases in areas that correspond to FEF (Bucher et al., 1997; Petit et al., 1995; Lang et al., 1994), supplementary eye field (SEF; Pierrot-Deseilligny et al., 1993), and parietal eye field (PEF; Pierrot-Deseilligny et al., 1995). The activations in the basal ganglia can be attributed to the basal ganglia–thalamo–cortical (ocular) motor loop (Alexander et al., 1986). Furthermore, brain activation studies have shown that cerebellar activations in the vermis and the hemispheres are also involved in ocular motor control (Dieterich et al., 2000; Miall et al., 2000; Stephan et al., 2002a). The unilateral activations found in the right prefrontal and parietal cortex may represent an increased level of alertness or sustained attention which occurs when the eyes are open. Sustained attention is thought to rely on both attention and arousal and is strongly lateralized in the right hemisphere (for review see Coull, 1998). Arousal can be defined as a state of physiological reactivity (Broadbent, 1971) that is thought to arise in the locus coeruleus and act on the reticular system as well as on the posterior attentional system. The latter consists of the posterior parietal cortex (PPC), the superior colliculi, and the thalamus (Posner and Petersen, 1990); it has a well-established role in orienting to visual locations.

Brain activation studies have consistently localized an amodal system for sustained attention in the frontal and parietal lobules, i.e., in the DLPFC, FEF, and the PPC, predominantly in the right hemisphere. These areas become activated in response to sustained attention in multisensory as well as visual, somatosensory, and auditory experimental setups (Pardo et al., 1991; Paus et al., 1997). The right posterior parietal cortex is involved in attentional orientation to locations (PET: Corbetta et al., 1993; Nobre et al., 1997) and is considered critical for forming a multimodal sensory representation of the extrapersonal space (Mesu-

lam, 1981). Earlier brain activation studies reported that the FEF and SMA (including SEF) are also involved in visuospatial attentional tasks (Nobre et al., 1997; Coull et al., 1996) and that the thalamus is implicated in sustained attention (PET: Kinomura et al., 1996; Paus et al., 1997). Furthermore, the anterior insula, which was also activated in our study, is involved in covert shifts of attention (Gitelman et al., 1999).

*An "interoceptive mental state" (eyes closed > eyes open)?*

The cortical activation of various sensory systems seems to prevail in the eyes-closed state. This is reflected by signal increases in areas that represent the visual (van Essen, 1979; Garey, 1990), somatosensory (Fox et al., 1987), vestibular (Guldin and Grüsser, 1998; Brandt and Dieterich, 1999), and auditory systems (Webster and Garey, 1990). Earlier visual imagery studies also reported that frontopolar areas exhibit bilateral activation, which can be attributed to imagination (Mellet et al., 1998; Lamm et al., 2001).

It is conceivable that multisensory cortex activations reflect imagination during the recall of sensory experiences. Imagination seems to activate the same brain structures within the same modality as actual perception (Kosslyn et al., 2001). In fact, imagery of various sensory stimulations and ocular motor performances activate areas that overlap with those activated under "real" conditions such as acoustic (Yoo et al., 2001; Halpern and Zatorre, 1999), visual (Mellet et al., 1998; Wexler et al., 1998), and ocular motor areas (Bodis-Wollner et al., 1997; Law et al., 1997). Our study strikingly showed that several sensory modalities were activated simultaneously in single subject and group analyses.

Although more ocular motor activity was found in the eyes-closed condition, activation of cortical and basal ganglia ocular motor structures was greater during the eyes-open condition. Because the registered eye movements were mainly involuntary pendular deviations rather than voluntary saccades and pursuit, one can assume that such eye movements do not require cortical control by basal ganglia–cortical loops. In contrast, the opening of the eyes is associated with the attempt to gather visual information and fixate expected targets; hence it may activate the cortical ocular motor system.

In conclusion, the state chosen as rest condition may have a considerable impact on the interpretation of brain activation studies. This means that with the eyes-closed state as rest condition, the mere opening of the eyes results in task-independent "deactivations" of the visual cortex. Largely task-independent decreases have been recognized earlier for different cognitive, motor, and sensory paradigms (Raichle et al., 2001; Mazoyer et al., 2001). Our data suggest that the differential effects of eyes-open vs eyes-closed conditions reflect two different states of mental activity: an "interoceptive" state with the eyes closed, characterized by imagination and sensory activity, and an "exteroceptive" state with the eyes open, characterized by activation of attentional and ocular motor structures.

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