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Abbreviations:
AC = anterior commissure
PC = posterior commissure
PET = positron emission tomography
ROI = region of interest
SPECT = single photon emission computed tomography

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Cognitive Stimulation with the Wisconsin Card Sorting Test: Functional MR Imaging at 1.5 T[1]

PURPOSE: To determine whether functional magnetic resonance (MR) imaging can demonstrate a specific pattern of cerebral activation during cognitive stimulation by using a high-level cognitive task such as the Wisconsin Card Sorting Test.

MATERIALS AND METHODS: Thirty-one healthy volunteers underwent functional MR imaging with a 1.5-T MR imager with a standard head coil (100/50 [repetition time msec/echo time msec], 230-mm field of view, 40° flip angle, 256 × 256 matrix). For stimulation, a personal computer version of the Wisconsin Card Sorting Test was used. Image analysis was done off-line, and cross-correlation coefficients between the stimulus function and the signal intensity response were calculated on a pixel-by-pixel basis and overlaid onto the corresponding anatomic MR image for each volunteer.

RESULTS: Stimulation resulted in strongly frontal activation, which included the mesial and the dorsolateral prefrontal cortexes, interconnected with Brodmann areas 44, 45, and 46. While activation was often bilateral, the largest area of activation was in the right hemisphere. Activation also was found in the basal ganglia and the mesial thalamic nuclei.

CONCLUSION: Functional MR imaging can demonstrate a specific pattern during activation with a cognitive task. Functional MR imaging has promise for more precise anatomic and functional imaging studies of brain interaction than have other imaging modalities.

Functional magnetic resonance (MR) imaging is a recent, noninvasive technique for evaluating brain function (1–4). High spatial resolution (5) and independence from any exogenous radioactive tracer are advantages of functional MR imaging as compared with other imaging modalities, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). A further advantage is the simultaneous acquisition of activation and topographic data. Functional MR imaging helps measure regional increases in MR signal intensity during brain activity.

To explain these regional changes, previous investigators suggested that local cortical activation leads to an increase in both regional blood flow and blood volume, which in turn overcompensates for the increase in oxygen use (6). The result is a locally decreased concentration of paramagnetic deoxyhemoglobin at the capillary venous level and, therefore, a smaller susceptibility difference between venous blood and brain parenchyma, which leads to a local signal intensity increase on gradient-echo images (7). This so-called blood oxygenation-level–dependent, or BOLD, effect depends on magnetic field strength (8,9). Signal intensity and signal intensity fluctuation increase in proportion to field strength (2,10,11). Functional MR imaging at 1.5 T seems to be an acceptable compromise (12–17).

To the best of our knowledge, at the time this article was written, investigations had mostly demonstrated discrete areas of signal intensity change in response to complex visual, motor, auditory, and olfactory stimuli (3,18–20). Given its capability for producing high-spatial-resolution images, functional MR imaging also may contribute to a better understanding of functional anatomy in high-level cognitive tasks (21).

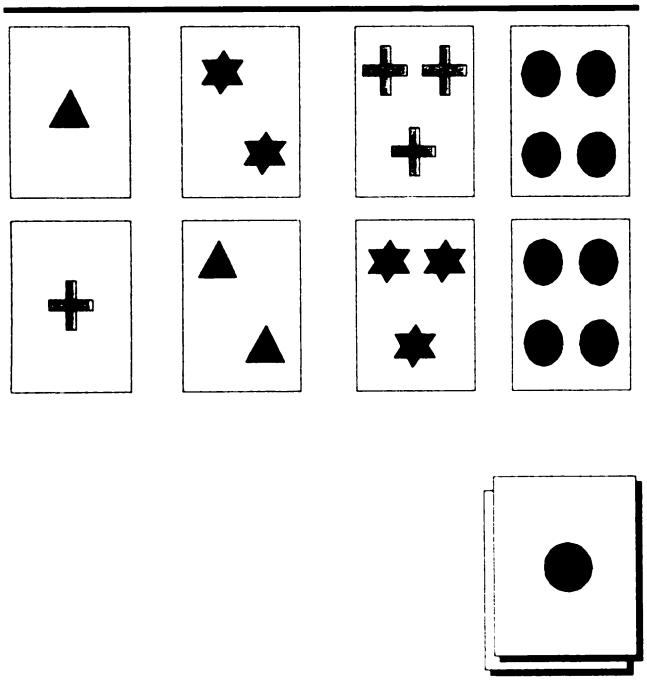

Figure 1. Wisconsin Card Sorting Test. Four reference cards are presented; an additional card has to be matched by the subject to one of the reference cards with respect to a sorting criterion, such as color, number, or shape.

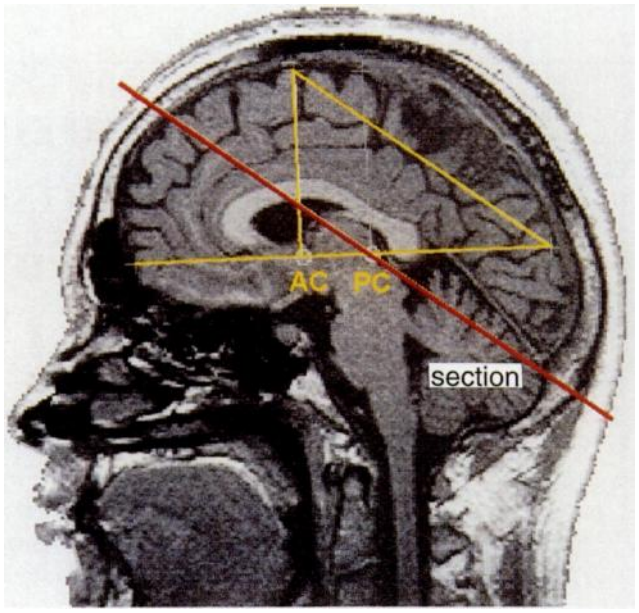

Figure 2. Spin-echo MR image (300/15) demonstrates the section position in the midline sagittal plane. The red line represents the single section used in the functional MR imaging examination. The yellow lines are subsidiary lines used during the planning of the final section.

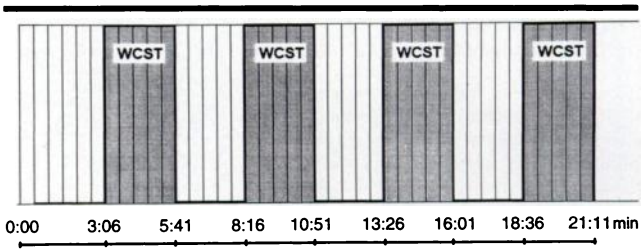

Figure 3. Graph shows time sequence during data acquisition. Each column represents a single image. There were four cycles of resting periods alternated with activation periods. *WCST* = Wisconsin Card Sorting Test.

The Wisconsin Card Sorting Test was used for cognitive stimulation in our study. This test is a well-known way to induce frontal cerebral stimulation (22–24). The task requires higher mental function (concept formulation, planning abilities, pertinent analysis of stimuli, self-elaboration of the strategy, maintenance of a concept) when processing the underlying principles of the card-sorting paradigm. Measurements of regional cerebral blood flow with xenon-133 SPECT or technetium-99m hexamethyl-propyleneamine oxime (or HMPAO) SPECT and PET with oxygen-15–labeled water have demonstrated frontal activation during the performance of this task (25). Our study was designed to address the following questions: (*a*) Can functional MR imaging reliably demonstrate activity during a high-level cognitive task such as the Wisconsin Card Sorting Test? (*b*) Are there differences between the localization of activated areas observed with functional MR imaging in this study and that observed with previous PET or SPECT studies by other authors?

MATERIALS AND METHODS

Subjects

Thirty-one right-handed, healthy volunteers (eight women, 23 men) with a mean age of 28.8 years ± 5.9 (standard deviation) and an age range of 21–38 years were recruited by means of advertisement. Written informed consent was obtained from all subjects. They were examined thoroughly for any internal, neurologic, or psychiatric disease. Inclusion criteria were no long-term drug intake, no past or present psychotherapy, and no use of psychotropic or cardiovascular medication. The study was approved by the ethical review board of the University of Jena, Germany.

Stimulation: Wisconsin Card Sorting Test

For stimulation, we used a personal computer version of the Wisconsin Card Sorting Test (STIM; Neuroscan, Sterling, Va). On the day before MR imaging, a 15-minute learning session took place to familiarize the volunteers with the whole test procedure.

The stimulus material was projected (model LC 2000; Philips Medical Systems, Eindhoven, The Netherlands) on a screen placed in front of the MR imager. The screen was made visible for the participants by placing an angled mirror on top of the head coil. Ear plugs were used to reduce the noise level. Foam pads and tapes were used to improve head fixation and prevent motion. Subjects used a hydropneumatic tap board with four buttons to take the test. The individual test performances were registered on-line.

The personal computer program displays a deck of playing cards according to the standard rules of the Wisconsin Card

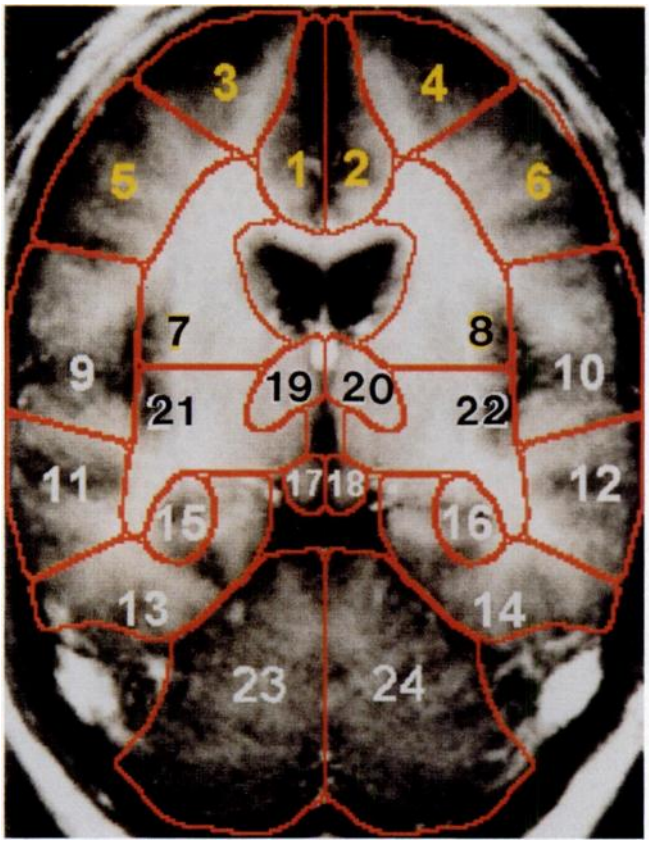

Figure 4. Positions of ROIs superimposed on the composite T1-weighted spin-echo anatomic section (300/15). ROI 1 (subject's right) and ROI 2 (subject's left) are in the dorsomedial part of the prefrontal cortex. ROIs 3 and 5 (subject's right) and ROIs 4 and 6 (subject's left) are in the dorsolateral part of the prefrontal cortex. ROI 7 (subject's right) and ROI 8 (subject's left) are located in the anterior part of the white matter. ROI 9 (subject's right) and ROI 10 (subject's left) are in the frontotemporal region. ROI 11 (subject's right) and ROI 12 (subject's left) are in the superior temporal gyrus. ROI 13 (subject's right) and ROI 14 (subject's left) are in the middle and inferior temporal gyri. ROI 15 (subject's right) and ROI 16 (subject's left) are in the hippocampus. ROI 17 (subject's right) and ROI 18 (subject's left) are in the midbrain. ROI 19 (subject's right) and ROI 20 (subject's left) are in the thalamus; ROI 21 (subject's right) and ROI 22 (subject's left) are in the posterior parts of the white matter. ROI 23 (subject's right) and ROI 24 (subject's left) are in the cerebellum.

Sorting Test (Fig 1). The computer deals four reference cards and presents an additional card that the subject must match with one of the reference cards. Each card shows a set of symbols consisting of triangles, stars, crosses, or circles in red, green, yellow, or blue. Each symbol can occur on the card one to four times. Each additional card presented can be sorted in three ways, according to the shape, color, or number of symbols on the reference cards. The computer indicates whether the choice was correct after each drawing. The card-sorting category changes without prior warning after eight consecutive correct trials in a given category. Sorting criteria are randomly selected by the personal computer program without the subject's knowledge.

Imaging Sequence

Imaging was performed with a 1.5-T MR imager (Gyroscan ACS II; Philips Medical Systems) with a standard head coil. Section selection was performed after acquisition of scout images with sagittal, transverse, and coronal orientations by using a spin-echo sequence (300/15 [repetition time msec/echo time msec], 90° flip angle, 3-mm section thickness). The straight line between the anterior commissure (AC) and the posterior commissure (PC) on a midline sagittal image (26) was used to determine the orientation and the location of the section used for functional imaging. The point where the line perpendicular to the AC-PC line through the AC crosses the parietal cerebral surface was determined. Next, the crossing point of the AC-PC line with the occipital cerebral surface was identified. The line parallel to these two reference points and traversing the posterior commissure determined the position of the section used for the functional MR imaging examination (Fig 2). It covered parts of the frontal lobe, the thalamus, the hippocampus, the temporal lobe, and the cerebellum.

This procedure ensures highly reproducible section orientation among different individuals in different sessions. A T1-weighted spin-echo sequence with the same orientation was performed to acquire high-resolution anatomic images (300/15, 230-mm field of view, 256 × 256 matrix, 3-mm section thickness, three sections). To establish the location of major vessels, a time-of-flight MR angiogram was acquired with the same orientation.

For functional imaging, a T2*-weighted gradient-echo sequence (100/50, 40° flip angle, 230-mm field of view, 256 × 256 matrix, 10-mm section thickness, 0.9 × 0.9 × 10 mm voxel dimensions) was used.

Each dynamic series consisted of 41 images and comprised four cycles of task performance and rest (Fig 3). The first image was discarded to allow MR signal intensity equilibrium. Five images were acquired during each resting period and each activation period. The acquisition time per image was 31 seconds. Subjects were instructed to keep their eyes open, count silently, and press the buttons in a self-paced, freely chosen rhythm during the resting periods. During the activation periods, they took the Wisconsin Card Sorting Test as described previously.

Data Analysis

Image analysis was carried out with a workstation (SPARCstation 20; Sun Microsystems, Mountain View, Calif) by using PV-WAVE (Visual Numerics, Boulder, Colo). The functional MR images were realigned to the first image of the dynamic series in each volunteer by using a least-squares algorithm. Motion was corrected by means of translation in the x (anteroposterior) direction and the y (left-right) direction and also by means of in-plane rotation α. The data sets for the 31 volunteers were motion corrected by using the three mentioned parameters. First, the mean correction and standard deviation were calculated for each subject; second, the mean ± standard deviation were calculated for the group.

For the analysis of data from individual subjects, the realigned images were smoothed with a Gaussian filter with a full width at half maximum of 4 mm. The cross-correlation coefficients for the predefined stimulus function and the signal intensity response of each pixel were calculated (27). A threshold of 0.3 was used for the cross-correlation coefficients (cor-

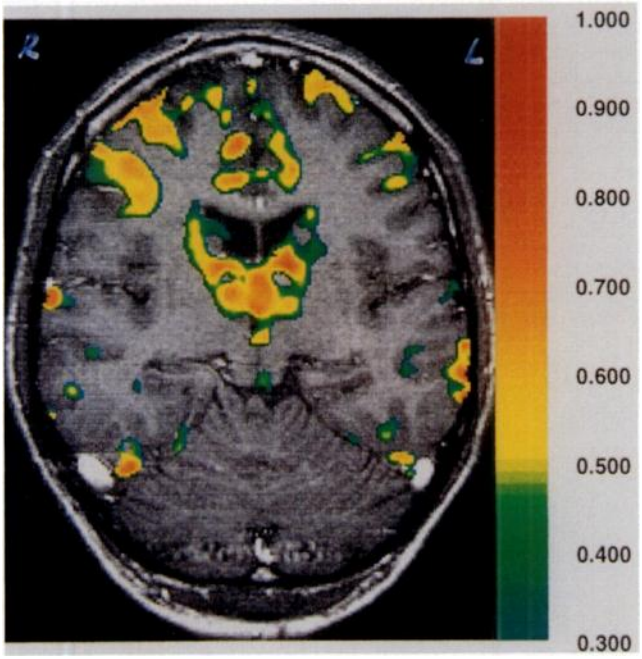

Figure 5. T2*-weighted fast-field-echo MR image (100/50, 40° flip angle) obtained at an examination of a 28-year-old man. The color-coded scale on the right represents the values of the cross-correlation between the ideal stimulus function and the measured activation.

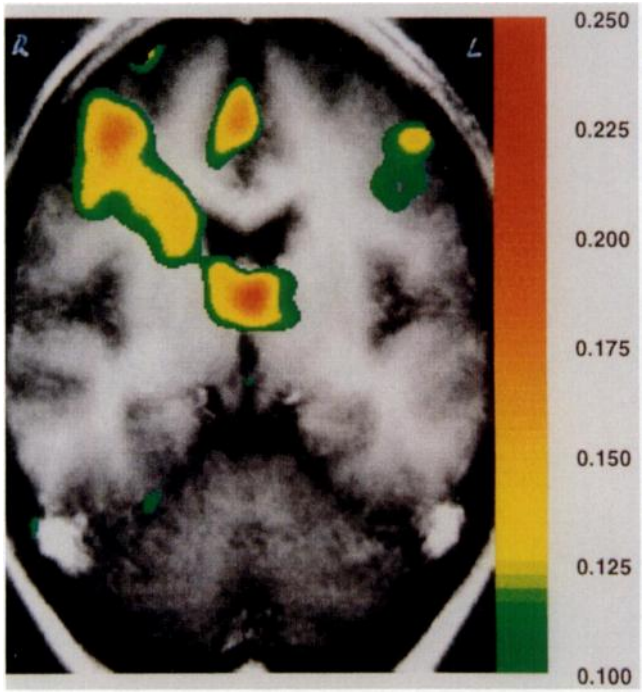

Figure 6. Composite correlation map composed from data in 31 volunteers. The composite correlation map was matched with the corresponding composite anatomic T1-weighted spin-echo section (300/15) of the volunteers.

responding to $P < .05$), which subsequently were overlaid onto the corresponding anatomic section.

To create a composite map for all volunteers, the correlation maps for each individual were standardized by using the maximum anteroposterior and left-right dimensions. Unlike in the analysis of data from individual subjects, a larger Gaussian filter with a full width at half maximum of 7 mm was applied. The normalized cross-correlation coefficient maps were averaged at each pixel to create a composite map for all volunteers. For each pixel, the mean of the Fisher *Z*-transformed cross-correlation coefficient of every single study was calculated and a threshold of 0.1 was used. This final correlation map was overlaid onto the corresponding anatomic section, which was standardized in the same way as described earlier.

Different regions of interest (ROIs) were selected for statistical testing before data analysis (Fig 4). Statistical testing was done in two steps. First, for each volunteer, the mean cross-correlation coefficients were calculated for each ROI and were used to determine overall statistical differences between the single ROIs by using the Friedman test. Second, the Bonferroni-adjusted Wilcoxon signed rank test was used to compare every single frontal ROI (ROIs 1–8) versus the remaining ROIs (ROIs 9–22), with the exception of those in the cerebellum. Furthermore, the right frontal ROIs were combined and compared with the corresponding combined contralateral ROIs to evaluate lateralization effects.

RESULTS

All 31 volunteers tolerated the study without problems. They performed the task easily. Evaluation of the test performance revealed, on average, 55 trials administered ± 10.6 (standard deviation), 16 errors ± 9.82, 11 perseverative responses ± 13.8, and 8.8 perseverative errors ± 9.68.

The mean parameters used for the motion correction per image were 0.863 mm ± 0.326 in the x direction, 1.293 mm ± 0.484 in the y direction, and a rotation α of 0.456° ± 0.208. Increases in the MR signal intensity synchronized with the performance of the task were observed with a preponderance in the right prefrontal area. A single representative example from one volunteer is presented in Figure 5.

The correlation maps of all volunteers were superimposed and projected on a matched average anatomic MR image. Activation was clearly localized in the right mesial and dorsolateral prefrontal cortexes, as it was in most individual examinations. A minor activation area also was detected in central regions representing the mesial thalamic nuclei. The cross-correlation coefficients ranged from 0.1 to 0.3 (Fig 6).

The signal intensity response of the single pixel showing maximum activation in ROI 1 averaged over all volunteers indicated a clear "on-off" phenomenon of the signal intensity–time course in accordance with the predefined stimulus function (Fig 7).

The Friedman test results indicated highly significant ($P < .001$) differences existed between the single ROIs. The Bonferroni-adjusted Wilcoxon signed rank test results for every single frontal ROI (ROIs 1–8) versus the remaining ROIs (ROIs 9–22), with the exception of those in the cerebellum, are presented in Table 1. The Bonferroni-adjusted Wilcoxon signed rank test results confirmed that the activation was lateralized to the right frontal brain regions (Table 2).

DISCUSSION

Performance of a cognitive task (ie, the Wisconsin Card Sorting Test) caused an increase in MR signal intensity in the frontal cortical areas. These areas included the mesial and the dorsolateral

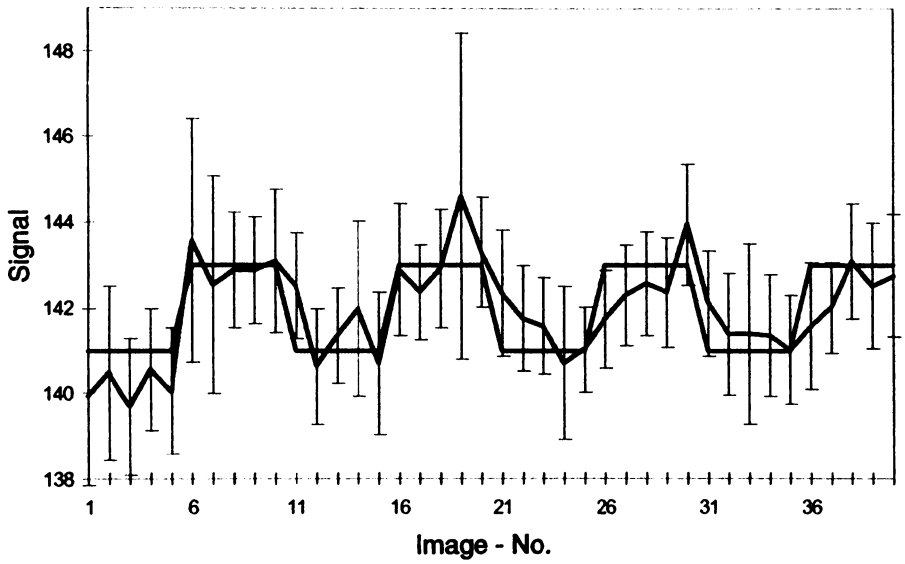

Figure 7. Graph shows signal intensity response of the pixels showing maximum activation in ROI 1 averaged over all 31 volunteers. Error bars = standard deviations. *Image-No.* = number of dynamic images, green line = ideal stimulus function, red line = averaged signal intensity response.

TABLE 1
Prefrontal Activation: Statistical Comparison of the Predefined ROIs

ROI Compared with ROIs 9–22	*P* Value
1	<.1
2	>.1
3	>.1
4	>.1
5	<.01
6	<.1
7	<.001
8	>.1

Note.—The Wilcoxon signed rank test with Bonferroni correction was used. Data were collected in all 31 volunteers.

TABLE 2
Lateralization: Statistical Comparison of the Predefined ROIs

ROIs Being Compared	*P* Value
1 vs 2	<.05
3 vs 4	<.1
5 vs 6	>.1
7 vs 8	>.1
9, 11, 13, 15, 17, 19, 21 vs 10, 12, 14, 16, 18, 20, 22	>.1

Note.—The Wilcoxon signed rank test with Bonferroni correction was used. Data were collected in all 31 volunteers.

prefrontal cortexes, corresponding to Brodmann areas 44, 45, and 46; areas of the basal ganglia and the mesial thalamic nuclei also were stimulated. Signal intensity increased during the task performance and declined slowly during the resting interval. Potential artifacts caused by head movements, eye movements, and large blood vessels were investigated and excluded by means of special data analysis (see Materials and Methods). Blood vessels were identified on a time-of-flight MR angiogram, because it has been demonstrated that relatively large venous vessels close to the brain surface also can give rise to functional effects (14).

Our results are in good overall agreement with previous PET and SPECT study findings (23,24,28–31). In accordance with these study findings, we found activation often bilaterally distributed. However, the largest activation area was observed in the right hemisphere in our study. Thus, the issue of lateralization still seems to be far from clear. Its controversy has been discussed in the literature. In a recent review, Goldberg and Podell (32) summarized the results of several functional brain imaging studies. There was no agreement about lateralization among different studies. For example, Marenco et al (24) reported a right-sided lateralization of frontal activity in healthy volunteers, which proved to be statistically significant. Whereas Berman et al (28) found a pronounced activation in the left dorsolateral prefrontal cortex, the area with maximum activation was in the inferior frontal gyrus bilaterally. Moreover, Graae et al (33) and Steinberg et al (34) could not detect frontal activation by using the Wisconsin Card Sorting Test for stimulation.

One limitation of our study is due to the single-section technique used: Only parts of the total volume of the frontal cortex were imaged. This might explain the discrepancy between the study findings of Berman et al (28) and our findings. In the former study, the sections were oriented parallel to the canthomeatal line containing the inferior frontal gyrus, whereas in our study it was mostly parts of the middle frontal cortex that were covered. Therefore, the possibility of a reversed pattern of lateralization in the more caudal parts of the prefrontal cortex cannot be excluded. van Horn et al (31) reported in their O-15 PET study a right-sided lateralization effect only for the inferior part of the superior frontal gyrus and not for other frontal brain regions. Thus, right-sided lateralization of activation might be confined to the superior and middle frontal gyri. In principle, this discrepancy between the findings of Berman et al (28) and our findings could be resolved by using three-dimensional functional MR imaging techniques, such as echo-planar imaging. However, to the best of our knowledge, no examination in which the Wisconsin Card Sorting Test was used with this technique has been published.

That we observed clearly lateralized activation may be due to the higher spatial resolution of functional MR imaging, as well as to the different analysis techniques used in PET and SPECT studies and in our study. In PET and SPECT, only pixels with a high absolute increase in signal intensity will result in a statistically significant signal intensity difference at activation. If one given pixel shows a high resting-state activity, the probability of inducing a statistically significant signal intensity increase will be reduced owing to certain ceiling effects. A recently developed analysis method, that is, statistical parametric mapping, may overcome this drawback of former PET analyses (35). In our study, not only are absolute signal intensity changes used in the functional MR imaging analysis, but also the time-dependent correlation of signal intensity changes with the predefined stimulus function is taken into account. Thus, the temporal locking between stimulus and response plays an important role in the analysis.

Considering this fact, the lack of lateral-

ization in most Wisconsin Card Sorting Test studies performed to date could have been due to the particular imaging and analysis technique used. Thus, functional MR imaging provides a promising tool for more precise anatomic and functional brain imaging.

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