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Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test — a functional MRI study on healthy volunteers and schizophrenics

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Abstract

It has been demonstrated by single photon emission computed tomography (SPECT) and positron emission tomography (PET) that frontal brain regions are stimulated during performance of the Wisconsin Card Sorting Test (WCST). The WCST is also regarded as one of the standard tests for the assessment of frontal activity in brain imaging studies of schizophrenia. In this study cerebral activation was assessed by means of functional magnetic resonance imaging (fMRI). In healthy volunteers WCST stimulation resulted in a right lateralized frontal activation. In 13 chronic schizophrenics on stable neuroleptic medication, a lack of activation in the right prefrontal cortex and — as a trend — an increased left temporal activity during execution of the WCST was noted compared to controls. Since a one-slice technique was used, no information about the activation pattern in adjacent brain regions was obtained. However, as fMRI possesses a superior spatial resolution compared to SPECT and PET, the anatomical localization of the activation effect in the measured slice can be defined more precisely. Beside these methodological considerations, the results are discussed in relation to prior findings of a reduced ability of schizophrenics to coordinate cerebral function. © 1997 Elsevier Science Ireland Ltd.

Keywords: Schizophrenia; Functional brain imaging; Cognitive stimulation; Hypofrontality

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1. Introduction

At present, functional imaging studies in schizophrenia have demonstrated three main findings: (1) hypofrontality; (2) altered basal ganglia perfusion or metabolism; and (3) altered temporal lobe perfusion or metabolism (Woods, 1992; Ebmeier, 1995). With regard to hypofrontality, the performance of a task specific for frontal lobe function during the scanning procedure facilitates the detection of the abnormality (Andreasen et al., 1992). Hypofrontality measured while performing such a specific task has also been called 'behavior-specific hypofrontality'.

In this context, the Wisconsin Card Sorting Test (WCST) has gained particular prominence for measuring frontal lobe function since Milner's work (Milner, 1963, 1971) on leukotomized epileptic patients. As Marenco et al. (1993) stated, the WCST involves 'working memory' and the ability to adapt behavior based on performance feedback. The task requires that the subject discovers classification principles. Once such a principle has been successfully established, the classification rule changes unexpectedly, and the subject has to dispense with the old and determine the new classification principle. Many studies have confirmed the usefulness of this test for the assessment of frontal lobe function in neurological and psychiatric patients (Fey, 1951; Drewe, 1974; Malmo, 1974; Robinson et al., 1980; Kolb and Whishaw, 1983; Stuss et al., 1983; Goldberg et al., 1987), although the specifity and validity of the WCST for frontal lobe functions has also been questioned (Anderson et al., 1991; Axelrod et al., 1996).

Various brain imaging techniques have been used to demonstrate prefrontal activation during the performance of this task: (1) measurement of regional cerebral blood flow (rCBF) with cortical probes using xenon 133, single photon emission computed tomography (SPECT) with xenon 133 or with *d,l*-hexamethyl-propylene amine oxime marked technetium-99m (^{99m}Tc-HMPAO-SPECT) and positron emission tomography (PET) with oxygen 15-labeled water; and (2) detection of cerebral glucose utilization which is directly linked to neural activity by means of PET with ^{18}F-labeled deoxyglucose.

In schizophrenics the most consistent finding when using the WCST as a cognitive stimulus was a mostly bilaterally localized decreased activation in prefrontal areas in comparison to controls (Berman et al., 1986; Weinberger et al., 1986, 1988; Rubin et al., 1991; Andreasen et al., 1992; Berman et al., 1992; Weinberger et al., 1992; Berman et al., 1993; Parellada et al., 1994; Rubin et al., 1994). Only the group of Kawasaki using ^{99m}Tc-HMPAO-SPECT found no differences between schizophrenics and controls (Kawasaki et al., 1993).

In recent years functional magnetic resonance imaging (fMRI), a new brain imaging methodology, was developed. The principle is based on the different behavior of oxygenated and deoxygenated hemoglobin (HbO_2 and $deHbO_2$) in the magnetic field: Neuronal activation causes an increase in local blood flow without a commensurate increase in oxygen extraction; thus, the $deHbO_2$ concentration is decreased. Since $deHbO_2$ is — in contrast to HbO_2 — paramagnetic, this leads to an increase of the local T_2^*-weighted magnetic resonance image signal (Himke et al., 1993). As $deHbO_2$ is used as an intrinsic contrast agent, the application of radioactive-labeled compounds is no longer necessary. Depending on the field of view, a resolution of up to 1 mm is possible, which overcomes the somewhat restricted spatial resolution of SPECT and also PET. A further advantage consists in the simultaneous acquisition of activation and topographical data. An overlap of two completely independent measures, as required in the case of SPECT and PET, is no longer necessary.

In order to evaluate cognitive stimulation effects in frontal brain areas, we performed the reported fMRI study. Our hypotheses were that: (1) frontal activation in healthy volunteers is detectable in fMRI following WCST stimulation; (2) fMRI allows for a more precise anatomical description of the activated areas when compared to other brain imaging techniques; and (3) schizophrenics are characterized by a missing frontal activation compared to controls.

2. Method

2.1. Subjects

Thirty-one right-handed volunteers (23 males, eight females) with a mean age of 28.8 years (S.D. = 5.9), recruited by advertisement, and 13 right-handed schizophrenic inpatients (eight males, five females), mean age 31.54 (S.D. = 7.85), diagnosed according to DSM III-R (American Psychiatric Association, 1987), were investigated. Written informed consent was obtained from both groups; the volunteers had to be free from any psychotropic and cardiovascular medication, the patients free from any cardiovascular medication only. All probands were native German speakers and were not paid for their participation. All participants were screened thoroughly for internal and neurological symptoms; persons exhibiting such symptoms or with first-degree relatives showing severe neurological disorders were excluded. A history or presence of alcohol or drug abuse was a further exclusion criterion. The volunteers were thoroughly screened for psychiatric illnesses. Persons exhibiting any symptoms or with first-degree relatives showing psychiatric disorders were excluded. The study was approved by the ethical review board of the University of Jena.

All patients were on stable neuroleptic medication (10 mg haloperidol or equivalent; mean chlorpromazine equivalent dose: 476.18, S.D. = 246.18). Psychopathology was rated by independent psychiatrists using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Clinical Global Impression (CGI) (National Institute of Mental Health, 1970), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The mean psychopathological rating scale scores were: CGI, 4.85 (S.D. = 0.90); BPRS, 37.54 (S.D. = 9.23); SANS, 49.31 (S.D. = 18.61); SAPS, 6.00 (S.D. = 5.48). The psychopathological ratings were performed by two experienced psychiatrists (HPV, FH) with an interrater reliability > 0.9.

2.2. Stimulation

For stimulation we used the stim®-PC-version of the WCST (Neurosoft Inc., 1990) and projected the material via a Philips LC 2000 projector® on a screen placed in front of the MRI scanner. By means of an angled mirror, placed above the head coil, the screen became visible for the participant. The subjects responded with their right hand by using a hydropneumatic tap-device with four buttons. The ears were plugged with wax in order to reduce the noise level in the scanner. On the day before the fMRI measurement, a learning session of 15 min took place during which the probands were familiarized with the whole test procedure.

The computer program incorporates a deck of cards according to the standard rules of the WCST. Each card carries a uniform set of symbols consisting of triangles, stars, circles, or crosses in red, green, yellow or blue. Each symbol can occur on the card one to four times. The deck of cards can be sorted in three ways with respect to shape, color or number of symbols that the cards carry. For administration of the test, the computer deals four reference cards and proceeds to present the participant with a further card that must be matched with one of the four reference cards. After each sort, the computer gives a feedback, as to whether the sort was correct or not. Sort criteria are selected by the computer on a random basis without the subject's knowledge. The card sorting category changes without prior warning after eight cumulative correct sorts in a given category.

2.3. Scanning procedures

Each 41-image series consisted of four baseline periods, during which subjects rested (eyes open, tapping the response device in a freely chosen rhythm) alternating with periods during which the WCST was performed. The experiment consisted of two conditions: first, the subject was asked to tap (baseline); five images were sampled. Second, during the WCST, another five images were sam-

pled. This sequence was repeated four times. Each series began with one image at rest (31 s) allowing MRI signal equilibrium to be reached, followed by 40 images during which activation alternated with baseline periods every 2.35 min (see Fig. 1).

Imaging was performed on a 1.5-T (Philips Gyroscan ACSII, Hamburg, Germany) MR tomograph using a standard head coil. For functional imaging, a T_2^*-weighted gradient-echo sequence (FFE) was used (echo time: 50 ms, repetition time: 100 ms, field of view: 230 mm, matrix: 256×256, slice thickness: 10 mm, voxel dimension: $0.9 \times 0.9 \times 10$ mm^3, flip angle: 40°). Scanning also included acquisition of high-resolution anatomical images for localization purposes (T_1-weighted, echo time: 15 ms, repetition time: 300 ms, field of view: 230 mm, matrix: 256×256, slice thickness: 3 mm), localized in the same plane and center position as the T_2^*-weighted images.

In order to ensure that in different subjects the same region was measured, the following procedure was used: a series of scout images (an initial set of five sagittal, transversal and coronal slices) was acquired, followed by a series of sagittal slices parallel to the brain's true midline. In the midline plane, the straight line between the commissura anterior and posterior (AC–PC line) was used to determine orientation and localization of the plane used for functional imaging. The crossing points of a perpendicular to the AC–PC line through AC with the cerebral surface and of the AC–PC line with the cerebral surface were identified. A line parallel to these two reference points crossing PC determined the slice where our fMRI measurement took place (see Fig. 2).

This single 10-mm slice covered frontal lobe, thalamus, hippocampus, temporal lobe and cerebellum. This procedure ensures that scan orientation and localization are highly reliable across sessions and across individuals.

2.4. Data analysis

Image analysis was carried out on a SUN Sparcstation 20 using PV-Wave (Visual Numerics Inc, Boulder, CO, USA). First, the fMRI images were realigned to the first image using a least-squares algorithm. The motion was corrected using three parameters: translation x, translation y and rotation α. Probands whose images exhibited a maximal translation ≥ 2 mm or a maximal rotation $\geq 2°$ were not included in the study. The data sets of the remaining 31 controls and 13 schizophrenics were controlled for the amount of motion correction necessary using the three mentioned parameters. First, the mean of these motion parameters for each subject was calculated; second, the mean (and standard deviation) of the

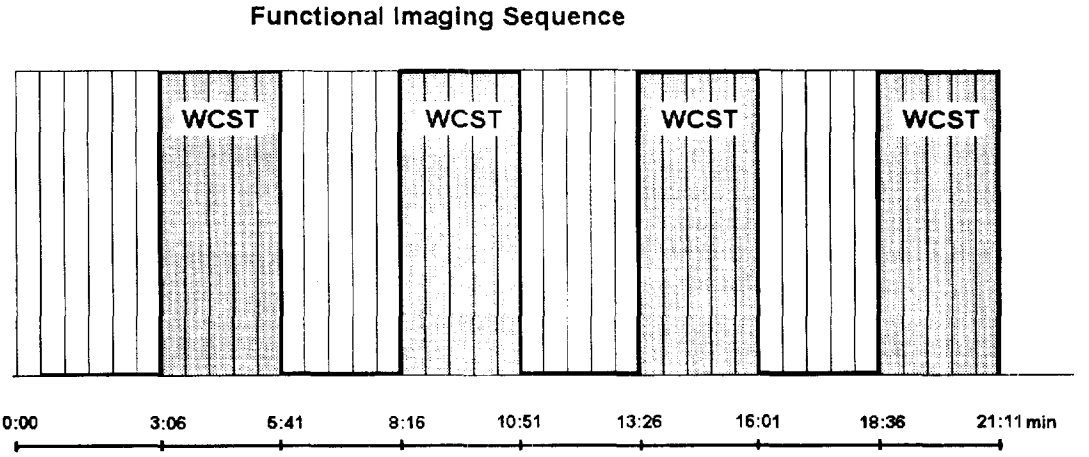


Fig. 1. Time sequence during data acquisition. WCST, Wisconsin Card Sorting Test.

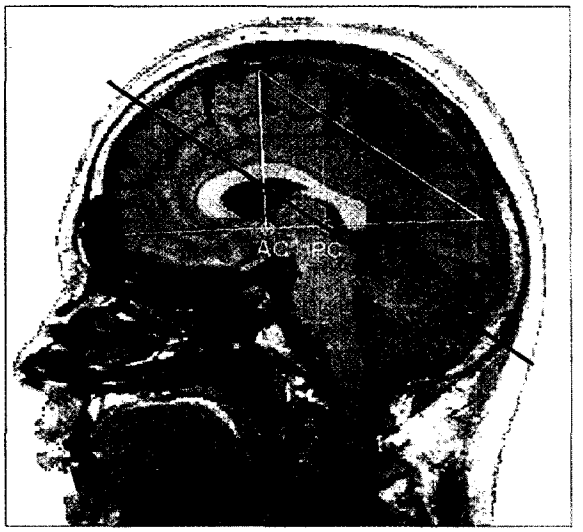
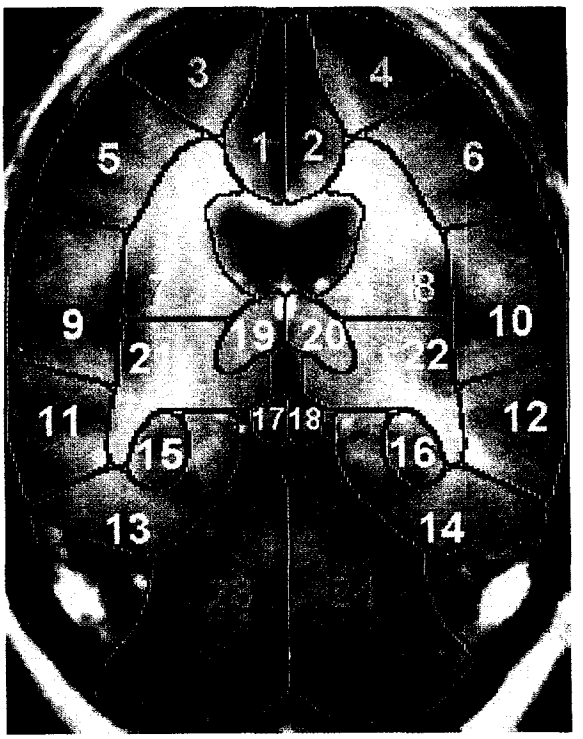


Fig. 2. Slice planning (T_1-weighted echo time: 15 ms; repetition time: 300 ms; field of view: 230 mm; matrix 256 × 256, slice thickness: 10 mm). AC, commissura anterior; PC, commissura posterior.



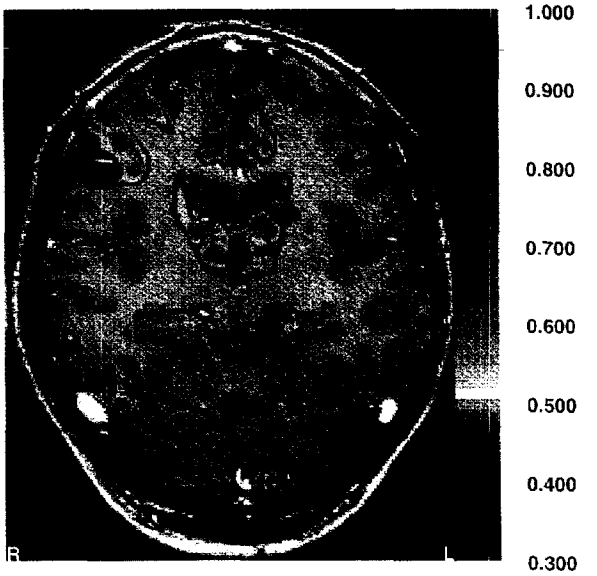


Fig. 4. Single experiment result (male control, 28 years) [T_2^*-weighted gradient-echo sequence (FEE), echo time: 50 ms; repetition time: 100 ms; field of view: 230 mm; matrix: 256 × 256; slice thickness: 10 mm; voxel dimension: 0.9 × 0.9 × 10.0 mm^3). On the right-hand side, the color-coded scale of the correlation coefficients is given.

obtained values was computed per group. In the results section, the respective values for both groups will be given.

For analysis of individual subjects, the realigned images were smoothed with a Gaussian filter with full width at half maximum (FWHM) = 4 mm. Then the correlation coefficients (CC) between the predefined stimulus function and the

Predetermined regions of interest (ROIs) overlaid on the standardized averaged anatomical slice of all subjects. The individual ROIs were labeled as follows: region 1, 2: prefrontal cortex, dorsomesial part; region 3, 4, 5, 6: prefrontal cortex, dorsolateral part; region 7, 8: white matter, anterior part; region 9, 10: fronto-temporal region; region 11, 12: temporal lobe (gyrus temporalis superior); region 13, 14: temporal lobe (gyrus temporalis medialis and inferior); region 15, 16: hippocampus; region 17, 18: midbrain; region 19, 20: thalamus; region 21, 22: white matter, posterior part; region 23, 24: cerebellum.

signal response of each pixel were calculated (Bandettini et al., 1993). The CCs of the individual examples were thresholded by 0.3 (corresponding to $P < 0.05$) and overlaid onto the corresponding anatomical slice.

Group analyses were performed by two different approaches:

1. Creation of a composite map for visual inspection.
2. Statistical testing of individual regions of interest.

A prerequisite for group comparison, besides reliable slice planning, is the normalization of the respective brain slice to a standard size. To this effect, the maximal distance of each brain slice in the anterior–posterior and left–right direction was used for standardization. Compared to the analysis of individual subjects, a larger Gaussian filter width of FWHM = 7 mm was applied.

To create a composite map of all individual subjects, the normalized CCs maps were averaged at each pixel. In order to calculate the mean of the CCs of all pixels, the CCs were Fisher's-Z-transformed and thresholded by 0.1. The correlation map obtained was overlaid onto the corresponding averaged anatomical map, standardized in the same way as described above.

For statistical testing, different regions of interest (ROIs) (see Fig. 3) were determined before data analysis. For each single subject the mean CC of each ROI was calculated and used for statistical testing.

For testing of significantly different activated ROIs within one group (control subjects or schizophrenics), first the Friedman test was used to identify whether overall differences exist or not, followed by the Bonferroni-adjusted Wilcoxon signed-ranks test for two related samples to find statistically significant differences regarding lateralization (e.g. ROI 1 vs. ROI 2) and differences

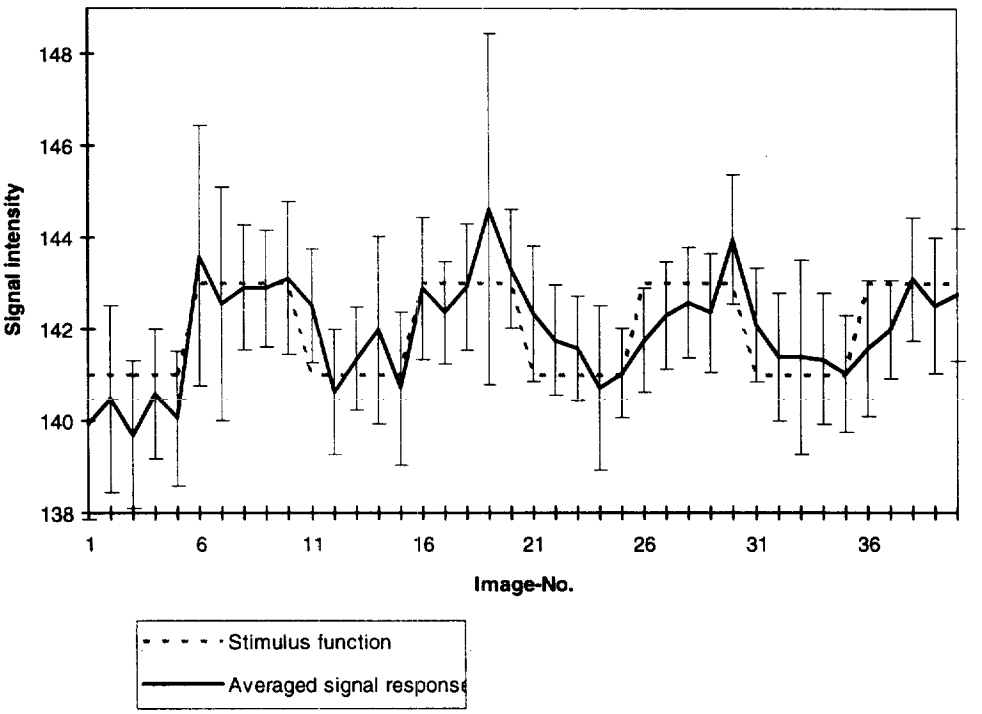


Fig. 6. Averaged signal intensity response (including standard deviations) of the pixel of maximal activation in ROI 1 of controls ($N = 31$).

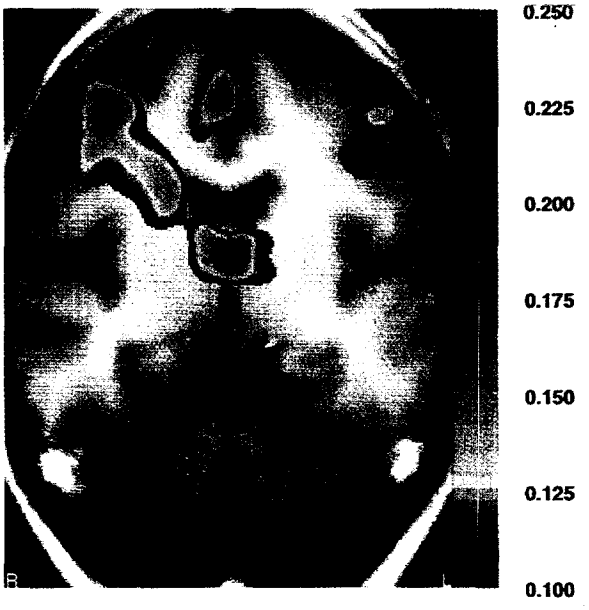


Fig. 5. Composite map matched onto the corresponding averaged anatomical slice of the control subjects ($N = 31$).

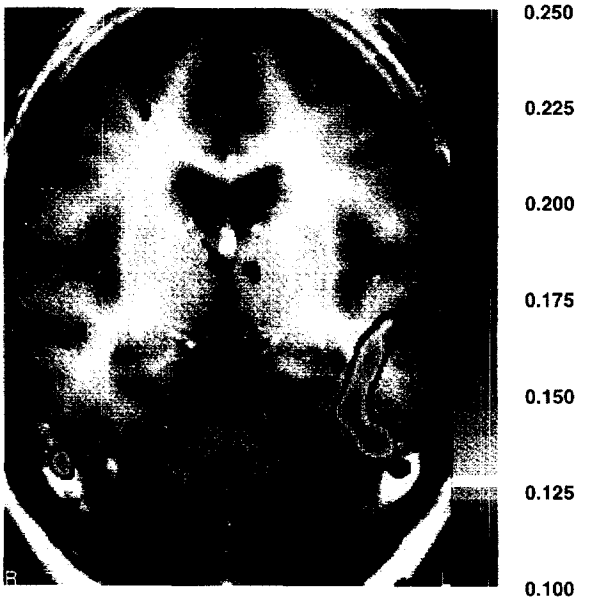


Fig. 8. Composite map matched onto the corresponding average anatomical slice of the schizophrenics ($n = 13$).

between frontal and the remaining ROIs (e.g. ROI 1 vs. ROIs 9–22).

To determine differences in the activation of the ROIs between schizophrenics and controls, a multivariate one-factor ANOVA (variables: mean CCs of each ROI of each subject) was applied.

In order to exploratively test differences in the activation status of the temporal ROIs in controls and schizophrenics, respectively, the t-test for unrelated samples was used.

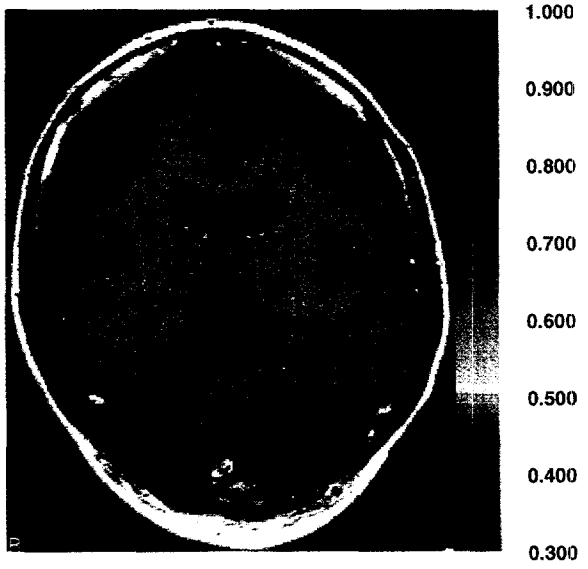


Fig. 7. Single experiment result (male schizophrenic, 27 years).

3. Results

3.1. Healthy volunteers

In most individuals a distinct activation with a preponderance in the right prefrontal area became obvious. A single representative example is given in Fig. 4.

All correlation maps were overlapped and projected on a matched and standardized anatomical slice (for detailed methodology, see above). As in most individual experiments, a clear activation (represented by overall correlation coefficients above 0.1) became apparent in the right mesial and dorsolateral prefrontal cortex (see Fig. 5).

Fig. 6 gives the average signal intensity response of the pixel of maximal activation in ROI 1 indicating a clear 'on–off' phenomenon of the

Table 1
Prefrontal activation in controls Statistical comparison of the predefined ROIs (Wilcoxon signed-ranks test with Bonferroni adjustment) in controls ($N = 31$)

Regions of interests (ROIs)	P-value
ROI 1 vs. ROI 9–22	< 0.1
ROI 2 vs. ROI 9–22	—
ROI 3 vs. ROI 9–22	—
ROI 4 vs. ROI 9–22	—
ROI 5 vs. ROI 9–22	< 0.01
ROI 6 vs. ROI 9–22	< 0.1
ROI 7 vs. ROI 9–22	< 0.001
ROI 8 vs. ROI 9–22	—

In schizophrenics ($N = 13$), no statistically significant differences or trends ($P < 0.1$) were obtained.

signal course in correspondence with the predefined stimulus function.

A minor activation was also detectable in central regions representing the medial thalamic nuclei.

The Friedman test resulted in a highly statistically significant result ($P < 0.0001$) indicating overall differences. Then, we tested the mean CC of every single frontal ROI (ROIs 1–8) vs. the averaged mean CC of the remaining ROIs (ROIs 9–22) with the exception of the cerebellum using the Bonferroni-adjusted Wilcoxon signed-ranks test. The result is presented in Table 1.

In order to further evaluate lateralization effects, the right frontal ROIs were compared with the corresponding left frontal ROIs using the Wilcoxon signed-ranks test with Bonferroni adjustment. For ROI 1 vs. ROI 2 a right > left activation was statistically significant ($P < 0.05$); for ROI 3 vs. 4 a trend ($P < 0.1$) became obvious.

3.2. Schizophrenics

In schizophrenic patients, a different pattern of activation was discernible. An individual example is presented in Fig. 7; the composite map of all schizophrenic patients is given in Fig. 8.

A missing activation in prefrontal areas became obvious in the schizophrenics. In analogy to the statistical approach used for the controls, the Friedman test was employed and yielded no statistically significant difference ($P = 0.07$). Every single frontal ROI (ROIs 1–8) was tested with the Wilcoxon signed-ranks test vs. the remaining ROIs with the exception of the cerebellum (ROIs 9–22). No statistically significant difference ($P < 0.05$) or trend ($P < 0.1$) was found.

3.3. Direct comparison: schizophrenics — control subjects

In order to directly compare the two samples, a multivariate ANOVA was performed. The result is summarized in Table 2.

It confirms the visual impression that schizophrenics in contrast to control subjects do not activate in the right prefrontal regions during WCST performance. In order to further validate this right-lateralized frontal activity difference in controls compared to schizophrenics, we analysed how many individual subjects in each group exhibited a right frontal activation defined as an at least 50% higher mean CC of ROIs 1, 3, and 5 than the mean CC of ROIs 2, 4 and 6 together with a mean CC of at least 0.1 in ROIs 1, 3 and 5. Seventeen of the 31 included controls (55%) and three of 13 schizophrenics (23%) followed this distribution, indicating that in fact a clear difference in right prefrontal activation existed between control subjects and schizophrenics.

Since visual inspection exhibited a left temporal activation in schizophrenics, but not in control subjects (see Figs. 5 and 8), the respective left temporal ROI (ROI 12) was compared in an exploratory manner between both samples using the t-test for unrelated samples. This resulted in a trend ($P < 0.1$), indicating that our study sample of schizophrenics was characterized by an increased left temporal activation compared to control subjects.

The mean motion correction per image in the x-direction was 0.863 mm (S.D. = 0.326) for control subjects and 0.957 mm (S.D. = 0.548) for schizophrenics; in the y-direction, 1.293 mm (S.D. = 0.484) and 1.306 mm (S.D. = 1.210), respectively; for the rotation, 0.456° (S.D. = 0.208) and 0.548° (S.D. = 0.437), respectively. So the amount of motion correction necessary was very comparable in both groups.

The WCST performance for both groups was as

Table 2
Multivariate ANOVA, schizophrenics vs. control subjects of predefined regions of interest (ROIs)

ROIs	CC mean (S.D.) Schizophrenics	Controls	*F*-value	Significance of *F*
ROI 1	−0.00533	0.10804	5.437	**0.025**
	(0.12238)	(0.13761)		
ROI 2	0.00939	0.05769	2.094	0.155
	(0.11833)	(0.12560)		
ROI 3	0.03017	0.06119	0.475	0.494
	(0.12819)	(0.12801)		
ROI 4	−0.01241	−0.00322	0.08	0.778
	(0.10446)	(0.10954)		
ROI 5	0.03906	0.11863	4.041	**0.051**
	(0.10316)	(0.12883)		
ROI 6	0.02347	0.08066	2.5	0.121
	(0.11207)	(0.12026)		
ROI 7	0.04104	0.09368	2.305	0.136
	(0.14060)	(0.08800)		
ROI 8	−0.00049	0.04780	1.481	0.230
	(0.10747)	(0.12039)		
ROIs 9–22[a]	0.01005	0.03081		
	(0.08591)	(0.07037)		

[a] Not included in the MANOVA.
CC, correlation coefficient.
Given are the mean correlation coefficients (CC) and standard deviations in brackets, the *F*-values and the significance level of the *F*-values (statistically significant differences are bold faced).
Degrees of freedom (d.f.) = 42.

follows: number of trials administered: control subjects, 55 (S.D. = 10.6), schizophrenics, 44 (S.D. = 14.9); total number of errors, 16 (S.D. = 9.82) and 19.8 (S.D. = 13.9), respectively; perseverative responses, 11 (S.D. = 13.8) and 13 (S.D. = 17.2), respectively; perseverative errors, 8.8 (S.D. = 9.68) and 9.82 (S.D. = 11.8), respectively. These results indicate a somewhat worse performance in schizophrenics compared to control subjects, but only reaching statistical significance for the total number of errors (*t*-test for unrelated samples, $P < 0.05$).

4. Discussion

4.1. Healthy volunteers

The first major finding was that the WCST stimulates mainly frontal areas in the measured slice. This corroborates earlier PET and SPECT studies (Weinberger et al., 1986; Berman et al., 1992; Kawasaki et al., 1993; Marenco et al., 1993; Rubin et al., 1994; Van Horn et al., 1996). Only Graae et al. (1991) and Steinberg et al. (1995) could not detect a frontal activation using the WCST as a cognitive stimulus.

We could furthermore demonstrate that the effect of stimulation is particularly pronounced in the right frontal lobe. The issue of lateralization during the WCST has been recently addressed by Goldberg and Podell (1995), stating that this test has failed 'to reveal any compelling lateralized patterns'. They therefore proposed another test, the Cognitive Bias Test (CBT), to further investigate possible lateralized patterns of frontal activation. Their statement was based on PET and SPECT studies using the WCST and indeed, when scrutinizing the available articles (see above), no constant lateralization pattern is discernible. One exception is the article published by Marenco et

al. (1993), using ^{133}Xe dynamic SPECT. In accordance with our work, they found a right-sided lateralization in healthy volunteers, which proved to be statistically significant, but the effect itself was not as pronounced as in our study. Marenco et al. (1993) discussed in detail the limitations of the SPECT methodology for precise localization of rCBF. Therefore, the only two PET studies published so far by Berman et al. (1991) and Van Horn et al. (1996) with the WCST as a cognitive challenge are important, since ^{15}O-PET should be more suitable to detect the spatial pattern of rCBF. Berman et al. (1991) found a more pronounced activation in the left dorsolateral prefrontal cortex [10.5% (S.D. = 2.5) left, 8.3 (S.D. = 2.0) right] with an activation maximum in the inferior frontal gyrus bilaterally. They reported results of slices localized between 6.5 and 8.5 cm above the canthomeatal line. This localization is not represented in the slice measured by us, which is located more apically, covering the middle and superior frontal gyrus. Therefore, the possibility of a reversed pattern of lateralized activation in the more caudal parts of the prefrontal cortex must be considered, although the number of volunteers investigated by Berman et al. (1991) is rather small ($N = 12$) in comparison to ours. In their $H_2^{15}O$-PET-study on 14 volunteers Van Horn et al. (1996) reported a right-sided lateralization effect only for the inferior part of the superior frontal gyrus, not for other frontal brain regions. Summarizing the results of these two PET studies and the findings presented here, right-lateralized activation might be confined to the superior and middle frontal gyrus. The discrepancy of our results and those of Berman et al. (1991), possibly caused by the different localization of the slices, could be resolved using three-dimensional fMRI techniques, such as echo planar imaging (EPI) fMRI. However, at present, no results with this technique have yet been reported.

The superior spatial resolution of fMRI might be one reason for the distinct lateralization effect found in the present study. Additionally, the different evaluation techniques of PET and SPECT in comparison to fMRI might play a role in explaining the divergent WCST study results obtained with these instruments. SPECT and PET analyses are based on the comparison of activation levels during rest and activation. Normally, a percent increase of the respective stimulus intensity is calculated. That means that only pixels with a high absolute increase in signal intensity can bring about a significant difference. If one given pixel possesses, for example, a high resting-activity, the possibility to induce an absolute signal increase which will be above the significance level is minimal due to a certain ceiling effect [Recently developed methods of analysis, i.e. statistical parametric mapping (Friston et al., 1995), may overcome this drawback of formerly used PET-analyses]. The fMRI analysis technique used in our study does not employ absolute signal intensity changes but the time-dependent correlation of signal intensity changes with the predefined stimulus function. Thus, not the absolute signal intensity change itself is decisive, but the time pattern in which it occurs. Very small signal intensity changes which possess a high correlation with the predefined stimulus function lead to a high activation in this pixel. Therefore, clearer results can be achieved, since the underlying activity during rest influences the activation pattern much less than in PET and SPECT. Keeping this in mind, the lack of lateralization in most WCST studies cited by Goldberg and Podell (1995) could have been due to the brain imaging techniques used up to now. Thus, fMRI provides a promising tool for more precise anatomical and functional brain imaging.

4.2. Schizophrenics

Our main result was a missing right frontal activation in schizophrenics compared to control subjects.

When scrutinizing the comparative studies of schizophrenics vs. control subjects (see Sec. 1), we found our results of a reduced or even missing frontal activation in schizophrenics to be in agreement with SPECT studies. With one exception (Kawasaki et al., 1993), all studies with the WCST as a cognitive challenge found a frontal decrease in rCBF in schizophrenics as compared to control subjects. Lateralization effects were

not reported with the exception of Rubin et al. (1994) who found a more pronounced right-sided rCBF-decrease in the superior prefrontal cortex in schizophrenics.

However, the strongly lateralized effect may be limited to the confined slice of measurement in our investigation. For regions above or below the measured slice, the activation pattern can be different. This was also true in the study of Rubin et al. (1994) who demonstrated pronounced differences between schizophrenics and controls in the right superior prefrontal cortex, but not in the inferior prefrontal regions and in the study of Van Horn et al. (1996), who showed a more pronounced right-sided activation in healthy volunteers in the superior frontal gyrus, but not in the middle or inferior part.

Since all our patients were on neuroleptics when investigated, we cannot determine whether the medication had a major impact on the obtained findings, but, as can be deduced from scrutinizing the already published articles dealing with this issue, this is not probable. The prefrontal reduction of rCBF during stimulation with the WCST was present in neuroleptic-free (e.g. Weinberger et al., 1986, 1988) as well as in neuroleptic-treated patients (e.g. Berman et al., 1986; Rubin et al., 1991, 1994).

The schizophrenics exhibited nearly the same mean WCST performance as the control subjects, which seems to be surprising. However, since only patients were investigated who were capable of being examined in the MR-scanner, this might represent a selection bias.

One might also argue that the schizophrenics would have exhibited the same result, i.e. no frontal activation during stimulation, if there was an increased frontal activation present already in the resting condition defined as eyes open and tapping the response device in a freely chosen rhythm. One way out of this problem would have been to introduce a third condition, 'absolute' rest, which was not possible since the schizophrenics did not tolerate the required 50% increase of the measurement period. Additionally, it does not seem probable that schizophrenics are hyperfrontal in both conditions. As mentioned, most studies found hypofrontality in schizophrenics during the performance of the WCST and there is no conclusive evidence in the literature of functional brain imaging studies that schizophrenics exhibit an increase in frontal activity during motor stimulation (e.g. Ebmeier, 1995).

A second finding was the increased left temporal activation in schizophrenics. This result, only reaching a trend, should not be overinterpreted, especially since such an activation has not been described in studies using the WCST as cognitive stimulus. In the resting state, however, Friston et al. (1992) could show in their PET studies that schizophrenics who exhibited marked signs of disorganization or reality distortion showed an increased activation in the left temporal region. During cognitive stimulation either with an internal word generation task (Liddle et al., 1994), a verbal fluency task (Yurgelun-Todd et al., 1996) or CPT (Schröder et al., 1996), a left temporal activation was found for subgroups of schizophrenics, not in control subjects. This pattern of activity might be interpreted as a result of a reduced ability of schizophrenics to produce an efficient focusing of cerebral activity, an indicator of a disturbed coordination between cerebral areas. The structural basis of this phenomenon may be the reciprocal connections between prefrontal and temporal brain regions (Goldman-Rakic, 1987, 1990). On the basis of these findings, Weinberger (1991) postulated that the primary defect of schizophrenics when performing the WCST is not located in prefrontal regions but in the functional connectivity of different brain areas including the temporal cortex.

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References

Anderson, S.W., Damasio, H., Hones, R.D., Tranel, D., 1991. Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. Journal of Clinical and Experimental Neuropsychology 13, 909–922.

Andreasen, N.C., 1983. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa City.

Andreasen, N.C., 1984. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa City.

Andreasen, N.C., Rezai, K., Swayze, V.W., II, Flaum, M., Kirchner, P., Cohen, G., O'Leary, D.S., 1992. Hypofrontality in neuroleptic naive patients and in patients with chronic schizophrenia. Assessment with xenon single-photon emission computed tomography and the Tower of London. Archives of General Psychiatry 49, 943–958.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised. American Psychiatric Press, Washington, DC.

Axelrod, B.N., Goldman, R.S., Heaton, R.K., Curtiss, G., Thompson, L.L., Chelune, G.J., Kay, G.G., 1996. Discriminability of the Wisconsin Card Sorting Test using the standardization sample. Journal of Clinical and Experimental Neuropsychology 18, 338–342.

Bandettini, P.A., Jesmanowicz, A., Wong, E.C., Hyde, J.S., 1993. Processing strategies for time-course data sets in functional MRI of the human brain. Magnetic Resonance in Medicine 30, 161–173.

Berman, K.F., Zec, R.F., Weinberger, D.R., 1986. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. Archives of General Psychiatry 43, 126–135.

Berman, K.F., Randolph, C., Gold, J., Holt, D., Jones, W., Goldberg, T.E., Carson, R.E., Herscovitch, P., Weinberger, D.R., 1991. Physiological activation of frontal lobe studied with positron emission tomography and oxygen-15 water during working memory task. Journal of Cerebral Blood Flow and Metabolism 11, S851.

Berman, K.F., Torrey, E.F., Daniel, D.G., Weinberger, D.R., 1992. Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. Archives of General Psychiatry 49, 927–934.

Berman, K.F., Doran, A.L., Pickar, D., Weinberger, D.R., 1993. Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cognitive activation. British Journal of Psychiatry 162, 183–192.

Drewe, E.A., 1974. The effect of type and area of brain lesion on Wisconsin Card Sorting Test performance. Cortex 10, 159–170.

Ebmeier, K.P., 1995. Brain imaging and schizophrenia. In: Boer, J.A., Westenberg, H.G.M., van Praag, H.M. (Eds.), Advances in the Neurobiology of Schizophrenia. Wiley, Chichester, pp. 131–156.

Fey, E.T., 1951. The performance of young schizophrenics and young normals on the Wisconsin Card Sorting Test. Journal of Consulting Psychology 15, 311–319.

Friston, K.J., Liddle, P.F., Frith, C.D., Hirsch, S.R., Frackowiak, R.S.J., 1992. The left medial temporal region and schizophrenia. A PET study. Brain 115, 367–382.

Friston, K.J., Homes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Human Brain Mapping 2, 189–210.

Goldberg, E., Podell, K., 1995. Lateralization in the frontal lobe: searching the right (and left) way. Biological Psychiatry 38, 569–571.

Goldberg, T.E., Weinberger, D.R., Berman, K.F., Pliskin, N.H., Podd, M.H., 1987. Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. Archives of General Psychiatry 44, 1008–1014.

Goldman-Rakic, P.S., 1987. The nervous system. In: Plum, F., Mountcastle, V.B., Geiger, S.R. (Eds.), The Handbook of Physiology: Higher Functions of the Brain. American Physiological Society, Bethesda, MD, pp. 373–417.

Goldman-Rakic, P.S., 1990. Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. In: Uylings, H.B.M., van Eden, D.G., De Bruin, J.P.C., Corner, M.A., Feensta, M.G.P. (Eds.), Progress in Brain Research: The Prefrontal Cortex — Its Structure, Function, and Pathology, vol. 85. Elsevier, New York, pp. 325–335.

Graae, E., Warkentin, S., Franzén, G., Risberg, J., 1991. Frontal lobe challenge: a comparison of rCBF during activation procedures. Journal of Cerebral Blood Flow and Metabolism 11, S372.

Himke, R.M., Hu, X., Stillman, A.E., Kim, S.-E., Merkle, H., Salmi, R., Ugurbil, K., 1993. Functional magnetic resonance imaging of Broca's area during internal speech. NeuroReport 4, 675–678.

Kawasaki, Y., Maeda, Y., Suzuki, M., Urata, K., Higashima, M., Kiba, K., Yamaguchi, N., Matsuda, H., Hisada, K., 1993. SPECT analysis of regional cerebral blood flow changes in patients with schizophrenia during the Wisconsin Card Sorting Test. Schizophrenia Research 10, 109–116.

Kolb, B., Whishaw, I.Q., 1983. Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. Journal of Nervous and Mental Disease 171, 435–443.

Liddle, P.F., Herold, S., Fletcher, P., Friston, K.J., Silbersweig, D., Frith, C.D., 1994. A PET study of word generation in schizophrenia. Schizophrenia Research 11, 168.

Malmo, H.P., 1974. On frontal lobe functions: psychiatric patient controls. Cortex 10, 231–237.

Marenco, S., Coppola, R., Daniel, D.G., Zigun, J.R., Weinberger, D.R., 1993. Regional cerebral blood flow during the Wisconsin Card Sorting Test in normal subjects studied by xenon-133 dynamic SPECT: comparison of absolute values, percent distribution values, and covariance analysis. Psychiatry Research: Neuroimaging 50, 177–192.

Milner, B., 1963. Effects of different brain lesions on card sorting. The role of the frontal lobes. Archives of Neurology 9, 90–100.

Milner, B., 1971. Interhemispheric differences in the localization of psychological processes in man. British Medical Bulletin 27, 272–277.

National Institute of Mental Health, 1970. Clinical Global Impressions. In: Guy, W., Bonato, R.R. (Eds.), Manual for the ECDEU Assessment Battery. Chevy Chase, Maryland, pp. 12-1–12-6.

Neurosoft Inc., 1990. User-Guide STIM card-sort. Sterling, USA.

Overall, J.E., Gorham, D.R., 1962. The Brief Psychiatric Rating Scale. Psychological Reports 10, 799–812.

Parellada, E., Catafau, A.M., Bernado, M., Lomeña, F., González-Monclús, E., Setoain, J., 1994. Prefrontal dysfunction in young neuroleptic-naive schizophrenic patients: a resting and activation study. Psychiatry Research 55, 131–139.

Robinson, A.L., Heaton, R.K., Lehman, R.A.W., Stilson, D.W., 1980. The utility of the Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. Journal of Consulting and Clinical Psychology 48, 605–614.

Rubin, P., Holm, S., Friberg, L., Videbach, P., Anderson, H.S., Bendsen, B.B., Strømsø, N., Larsen, J.K., Lassen, N.A., Hemmingsen, R., 1991. Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform disorder. A regional cerebral blood flow study. Archives of General Psychiatry 48, 987–995.

Rubin, P., Holm, S., Madsen, P.L., Videbach, P., Andersen, H.S., Bendsen, B.B., Strømsø, N., Larsen, J.K., Lassen, N.A., Hemmingsen, R., 1994. Regional cerebral blood flow distribution in newly diagnosed schizophrenia and schizophreniform disorder. Psychiatry Research 53, 57–75.

Schröder, J., Buchsbaum, M.S., Siegel, B.V., Geider, F.J., Lohr, J., Tang, C., Wu, J., Potkin, S.G., 1996. Cerebral metabolic activity correlates of subsyndromes in chronic schizophrenia. Schizophrenia Research 19, 41–53.

Steinberg, J.L., Devous, M.D., Moeller, F.G., Paulman, R.G., Raese, J.D., Gregory, R.R., 1995. Cerebellar blood flow in schizophrenic patients and normal control subjects. Psychiatry Research: Neuroimaging 61, 15–31.

Stuss, D.T., Benson, D.F., Kaplan, E.F., Weir, W.S., Naeser, M.A., Lieberman, I., Ferril, D., 1983. The involvement of orbito-frontal cerebrum in cognitive tasks. Neuropsychologia 21, 235–248.

Van Horn, J.D., Berman, K.F., Weinberger, D.R., 1996. Functional lateralization of the prefrontal cortex during traditional frontal lobe tasks. Biological Psychiatry 39, 389–399.

Weinberger, D.R., 1991. Hippocampal injury and chronic schizophrenia. Biological Psychiatry 29, 508–517.

Weinberger, D.R., Berman, K.F., Zec, R.F., 1986. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regonal cerebral blood flow evidence. Archives of General Psychiatry 43, 114–124.

Weinberger, D.R., Berman, K.F., Illowsky, B.P., 1988. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. Archives of General Psychiatry 45, 609–615.

Weinberger, D.R., Berman, K.F., Suddath, R., Torrey, E.F., 1992. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. American Journal of Psychiatry 149, 890–897.

Woods, S.W., 1992. Regional cerebral blood flow imaging with SPECT in psychiatric disease: focus on schizophrenia, anxiety disorders, and substance abuse. Journal of Clinical Psychiatry 53, 20–25.

Yurgelun-Todd, D.A., Waternaux, C.M., Cohen, B.M., Gruber, S.A., English, C.D., Renshaw, P.F., 1996. Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production. American Journal of Psychiatry 153, 100–205.