Acta Psychiatr Scand 2003: 108: 32–40
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ACTA PSYCHIATRICA SCANDINAVICA
ISSN 0001-690X

The Danish PET/depression project: cognitive function and regional cerebral blood flow

Ravnkilde B, Videbech P, Clemmensen K, Egander A, Rasmussen NA, Gjedde A, Rosenberg R, Gade A. The Danish PET/depression project: cognitive function and regional cerebral blood flow.
Acta Psychiatr Scand 2003: 108: 32–40. © Blackwell Munksgaard 2003.

Objective: To clarify the relationship between cognitive functions and regional cerebral blood flow (rCBF) in a large group of depressed patients compared with healthy controls.
Method: A set of principal components was extracted from scores of a battery of neuropsychological tests of 40 patients suffering from major depression and 49 healthy controls. The components were correlated by multiple linear regression analyses to selected regions of interest in the brain obtained from positron emission tomography images.
Results: In contrast to findings in the healthy controls, cognitive functions in the depressed patients correlated significantly with rCBF in specified regions of interest in only a few instances.
Conclusion: Our study indicates that disturbed cognitive functions in depression do not relate to specific areas of the brain in the same way as normal cognitive functioning, suggesting that the abnormalities of brain function in major depression may be qualitative, rather than quantitative, in nature.

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Key words: depression; cognition; regional blood flow; tomography, emission-computed; neuropsychological tests; magnetic resonance imaging

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Accepted for publication March 7, 2003

Introduction

Numerous neuropsychological investigations have concluded that cognitive deficits often accompany clinical depression, although these deficits may vary in severity (1). Neuroimaging studies of the biological substrates of major depression have identified both functional and structural abnormalities (2–6). Most of the previous imaging studies considered cerebral blood flow in the resting state while a few have used cognitive activation paradigms for investigation of the brain function in depressed patients (7–11). Fewer studies have investigated the relationship between neuropsychological findings and regional cerebral blood flow (rCBF) or clinical variables and rCBF in regions of interest (12–16).

In a positron emission tomography (PET)-study Bench et al. initially demonstrated that the cognitive disturbances generally observed in 40 depressed patients were inversely correlated with the blood flow to the left medial prefrontal cortex (13). In a subsequent study, Dolan et al. (12) extracted two principal components, a memory component and an attentional component, from the test scores obtained in a previous study of 29 depressed patients (17, 18). In this analysis, the attention component (ATC) correlated significantly with reduced rCBF in prefrontal areas [Brodmann areas (BA) 9, 10] and posterior areas (BA 40, 42, 43 and 39). The memory component was correlated with rCBF in the anterior cingulate cortex (BA 32, 24), the prefrontal cortex (BA 9,10), the precuneus, and posterior cingulate cortex (BA 31, 30 and 23) (6).

Using Single photon emission computed tomography (SPECT) Austin et al. (14) found associations between impairment of verbal memory and attention variables and increased blood flow to the posterior cingulate cortex in a group of depressed patients ($n = 49$) in comparison with a control group whereas Awata et al. (15) did not find any

correlation between cognitive functions and rCBF in 18 depressed patients.

These correlation studies point to neuropsychological impairment in depressed patients being related to rCBF mainly in cingulate and medial prefrontal areas but need replication. Thus, we decided to undertake an investigation of depressed patients and healthy controls including neuropsychological testing, psychiatric examination, and neuroimaging (PET and MRI scans) to clarify the relations between clinical, neuropsychological and neurobiological aspects of major depression in a large unselected group of depressed patients.

In a previous study, an extensive neuropsychological test battery was selected on the basis of existing research of patients with depressive illness and cognitive dysfunctions (1). The main areas covered with this battery were attention, memory and executive functions, and tests of verbal as well as non-verbal modalities were employed. Measures of premorbid intelligence were also presented. On the basis of this battery, widespread cognitive dysfunctions were observed among the depressed patients compared with matched controls, irrespective of age, gender, and education. The dysfunctions were not correlated with the severity of depression or antidepressant medication. Likewise, psychomotor retardation could not fully explain the results obtained from timed tests.

The two groups had also undergone PET scanning and patients showed increased blood flow to the hippocampus and the cerebellum compared with the matched controls (5). Furthermore, differences between patients and controls in the vermis bilaterally, the left amygdala, the right subgenual and right anterior cingulate gyrus, and the basal ganglia bilaterally were found (16). Blood flow to the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex correlated highly with psychomotor retardation in the patients.

The aim of the present study was to address the relationship between the neuropsychological measures and rCBF in the patient and the control samples. Hence, in a new analysis of the data a subset of measures from the original test battery was selected and transformed into principal components which were correlated with rCBF in particular regions of interest in the brain. In the light of the previous correlation studies of neuroimaging and cognition, we hypothesized that cognitive performance would be correlated with rCBF in specific regions of the brain in healthy volunteers and that specific cognitive deficits in patients would result in changed activity in these regions, especially in DLPFC, orbitofrontal cortex, anterior cingulate cortex and the hippocampus.

Material and methods

Subjects

In-patients between 18 and 70 years of age, fulfilling DSM-IIIR criteria for major depression according to a Structured Clinical Interview for DSM-IIIR (SCID-P) (19), were included in the study if they did not have a history of organic brain disease, drug or alcohol dependence or ongoing abuse. The latter was ensured by blood tests and urine samples of both patients and controls. Subjects were excluded from the study if any such condition was found or if the MRI scans showed any cerebral abnormality or generalized brain disease, except white matter lesions.

All patients scored 17 or more on the 17-item Hamilton Depression Rating Scale (20) or 9 on the subscale. Patients were rated at the inclusion in the project, immediately before the PET scans and 7 days later to ensure that the condition was stable.

Patients on psychotropic medication were also included in the study as our previous results and the results of others made it plausible that cognitive functions and patterns of blood flow would be dependent on the disease rather than on the medication (1, 13, 18, 21, 22).

The patients were found to be representative of patients with major depression when comparing their demographic data with data of all depressive patients admitted to the Psychiatric Hospital of Aarhus University Hospital during the study period (4). The diagnostic stability of the patients has furthermore been confirmed by a 5-year follow-up study based on patient records (11).

Control subjects were recruited through advertisement and interviewed in the same way as the patients to exclude any psychopathology. None of the healthy controls or their first-degree relatives had any history of psychiatric disorders, and steps were taken to ensure that controls did not have any medical disease involving the central nervous system. Controls with a history of previous or present abuse of psychotropic medication or alcohol were excluded. None of the controls were taking any psychotropic medication. At least one control was allocated for each patient matched for gender, age and, if possible, also for years of education. Patients as well as controls also underwent an extensive programme consisting of both physical and neurological examinations.

The study was approved by the Regional Scientific Ethics Committee for Aarhus County and by the Danish Data Surveillance Authority. All subjects gave written informed consent.

Principal components analysis

Details on the neuropsychological testing of patients and controls have been described previously (1). In this study, a subset of test measures from the original test battery was selected for further analysis (Table 1).

In order to reduce the number of correlations of rCBF with the regions of interest in the brain, scores on the individual tests were subjected to a principal components analysis (PCA). Six subsets of tests, representing different cognitive functions, were entered separately into this analysis based on *a priori* hypotheses of the inter-relationships of the tests in each subset. Prior to the PCA, all scores were transformed into *z*-scores with positive values indicating scores above average. The PCA was used to examine the relationship between tests within each subset and to transform the original set of variables into a smaller set of variables. In all cases the first principal component accounted for a major part of the variation among psychological tests according to the common criterion of choosing only principal components with eigenvalues above 1 (when using a correlation matrix) (23).

As the patients' test scores were influenced by their disease state we chose to enter only the control subjects' *z*-scores into the PCA. From this analysis we derived separate weightings for each test subsequently to be multiplied with the individual test scores of the patients. In this way the control sample was used as a 'normalized standard' for the neuropsychological tests applied. Studies have also shown that the relationship between the magnitude of rCBF and the level of cognitive performance is uncorrelated in depressed patients (9, 11). In order to validate the method applied, this relationship had to be tested in the control group. The six principal components derived from the subsets of tests entered into the separate analysis and the different weightings for each test are listed in Table 1. The percentage of variance explained by the first components was sufficiently high. The executive component was not submitted to the PCA as it comprised only one test [the Wisconsin Card Sorting Test (WCST) error score which is found to be the single measure most representative of this test]. Instead the *z*-scores on this particular test variable were used for correlations.

Table 1. Principal components, neuropsychological tests and the computed weightings (component score coefficients) based on the control group test scores

Principal component	Neuropsychological tests	Weightings	Total percentage of variance explained by the first component
General ability	DART	0.388	69.21
	WAIS-vocabulary	0.433	
	WAIS-information	0.379	
Attention	WAIS-digit symbol	–0.164	62.32
	Trail making – Part A	0.167	
	Trail making – Part B	0.173	
	Stroop test-colour naming	0.181	
	Stroop test-congruent	0.157	
	Stroop test-incongruent	0.175	
	Subtracting serial sevens	0.120	
	Brown – Peterson test	–0.116	
Verbal memory	Luria-verbal learning (retention)	0.344	78.76
	WMS-logical memory (immediate)	0.388	
	WMS-logical memory (delayed)	0.393	
Visual memory	WMS-R visual reproduction (immediate)	0.518	93.05
	WMS-R visual reproduction (delayed)	0.518	
Language	Phonological Verbal Fluency	0.597	70.19
	Semantic Verbal Fluency	0.597	
Executive function	Wisconsin card sorting – errors	*z*-score	

PET scanning

Details of the scanning procedure have been described elsewhere (5). The cerebral blood flow was mapped during rest using radioactive water ($H_2^{15}O$) in a Siemens Ecat Exat HR47 PET (Aarhus, Denmark). To account for diurnal variation in blood flow or symptoms, all scans were performed between 9:00 and 12:00 hours, and patients and controls were scanned in random order. One single frame of 40 s was acquired at the arrival of a bolus of 500 MBq (13.5 mCi) $H_2^{15}O$ to the brain. This was detected automatically at a true coincident count $>60\,000$.

The PET images were corrected for attenuation and scatter and filtered to 12 mm isotropic Full-Width-Half-Maximum. The whole brain image thus consisted of 47 slices.

MRI scanning

T1-weighted magnetic resonance (MR) images were used to coregister the subjects' brains to the coordinate system by Talairach & Tournoux (24) using an automatic algorithm with a linear 12 parameter fit. Furthermore, each subject's MR image was coregistered to the PET images from the resting state using the MINC-TRACC algorithm, with a linear six parameter fit. All coregistrations were validated visually and corrected manually using a reference point method if the automatic procedure had failed (5).

Image analysis and statistical correlations

From the atlas of Talairach & Tournoux (25), a template of 42 regions of interest was constructed on an average T1-weighted MR brain image of 305 normal subjects. The construction of the template and the advantages and disadvantages of the Regions-Of-Interest method in comparison with the Function-Of-Interest method have been described and discussed in detail by Videbech et al. (16). The radioactivity of every voxel was normalized to the total activity of all intracranial voxels in the entire brain to minimize the effects of intersubject variation of the global cerebral blood flow. The regions were then automatically applied to the PET images, which had been coregistered to the MR images. This application was performed without operator interference using a software program that calculated the total activity of every region.

Based on our hypotheses and on commonly accepted relationships between cognitive function and its presumed localization within the brain (26), a selection of brain regions was then chosen for correlation with the principal components. The correlations between each principal component and blood flow in selected regions were investigated using multiple linear regression controlling for age, gender, premorbid intelligence [by means of the Danish Adult Reading Test (DART)], and years of education. This regression analysis was carried out separately for patients and controls in three steps; (1) a crude analysis, (2) adding age and gender, (3) adding DART and years of education. When results were significant in either group, we performed a comparison of the slope between patients and controls by combining the two data sets in a linear regression to observe any significant differences between groups in that particular comparison. The level of significance adopted was $P < 0.05$, although we also report tendencies approaching ($0.05 < P < 0.10$). The results reported correspond to the fully adjusted level (step 3).

The amount of neuropsychological data was reduced by means of the PCA and brain regions were minimized by means of the regions of interest (ROI) method but the correlation data between principal components and rCBF were not subjected to further corrections for multiple comparisons because of the explorative nature of the study.

Data were analysed using the SPSS (9.0) software program.

Results

Forty patients and 49 controls entered the study. The two groups did not differ with respect to age, gender, social group and years of education (Table 2). Patients were moderately to severely depressed, measured by the 17-item Hamilton Scale of Depression (mean = 23.7, range 17–36). Twenty patients were unmedicated or had received antidepressant medication for < 1 week at the time of the study, and 20 patients had been treated longer than 1 week (medication-free, $n = 8$, SSRI, $n = 22$, tricyclic, $n = 10$). When comparing test performances in these two patient subgroups, no significant results were found. Similarly, no significant differences were observed when comparing unmedicated patients with patients treated with antidepressants (1).

Based on a previous analysis of the MR images, we ruled out the existence of any systematic differences such as atrophy between the control subjects and the patients (5).

Correlations with principal components and rCBF

The results of the control group are reported in Table 3 and of the patient group in Table 4.

General ability component. The general ability component (GAC) was tested for correlation with the prefrontal cortex, orbitofrontal cortex, BA 25, medial frontal gyrus, anterior cingulate gyrus, temporal cortex, cerebellum and the hippocampus. All regions were tested bilaterally.

The GAC of the control group was positively correlated with rCBF in the right orbitofrontal cortex ($P = 0.003$). There was also a tendency to a negative left temporal cortex correlation ($P = 0.057$). These results were significantly different from the patient group correlations with these regions ($P < 0.01$).

Patients' GAC scores tended to correlate positively with rCBF in the right hippocampus ($P = 0.052$) and the left hippocampus ($P = 0.087$). These results were significantly different from the control group correlations ($P < 0.01$).

Table 2. Sample description. Demographic variables (mean and SD) for the depressed sample and for controls

	Patients	Controls
	Mean (SD)	Mean (SD)
N	40	49
Age	41.6 ± 12.3	41.2 ± 11.6
Male/female	12/28	18/31
Years of education	11.7 ± 2.5	12.5 ± 2.4
Social group*	3.2 ± 1.8	3.5 ± 1.3

* Rated using the scale for socio-economic status in Denmark developed by the Danish National Institute of Social Research. The scale comprises five groups, group 1 having the higher rank.

Table 3. Significant results for the regression analyses of the principal components and regions of interest in the control group

	Crude		Age, gender		Age, gender, DART, edu		Patients vs. controls
Regions of interest	Slope	*P*	Slope	*P*	Slope	*P*	*P*
General ability							
Right orbitofrontal cortex	0.05	0.011	0.06	0.003	0.06	0.003	0.001
Left temporal cortex	−0.06	0.041	−0.06	0.054	−0.06	0.057	0.005
Attention							
Left anterior cingulate gyrus	0.02	0.016	0.01	0.035	0.01	0.039	0.000
Verbal memory							
Left hippocampus	0.02	0.348	0.02	0.158	0.03	0.084	0.002
Left caudate nucleus	0.04	0.031	0.04	0.011	0.04	0.023	0.002
Visual memory							
Right amygdala	−0.05	0.000	−0.05	0.001	−0.05	0.001	0.081
Left amygdala	−0.04	0.02	−0.03	0.024	−0.03	0.043	0.075
Right temporal cortex	−0.05	0.071	−0.07	0.016	−0.06	0.031	0.062
Left temporal cortex	0.06	0.064	0.06	0.034	0.06	0.066	0.086
Right anterior cingulate	−0.02	0.107	−0.02	0.066	−0.02	0.051	0.112
Right posterior cingulate	−0.02	0.142	−0.02	0.142	−0.03	0.047	0.064
Left posterior cingulate	−0.02	0.119	−0.02	0.142	−0.02	0.064	0.022
Right angular gyrus	−0.04	0.224	−0.04	0.028	−0.04	0.025	0.056
Language							
Right prefrontal cortex	0.05	0.007	0.04	0.047	0.04	0.056	0.000
Executive function							
Left temporal cortex	0.86	0.09	0.98	0.034	0.93	0.056	0.88
Right cerebellum	0.05	0.008	0.05	0.016	0.05	0.007	0.863

Table 4. Significant results for the regression analyses of the principal components and the regions of interest in the patient group

	Crude		Age, gender		Age, gender, DART, edu.		Patients vs. controls
Regions of interest	Slope	*P*	Slope	*P*	Slope	*P*	*P*
General ability							
Right hippocampus	0.06	0.021	0.05	0.052	0.04	0.052	0.001
Left hippocampus	0.05	0.025	0.05	0.088	0.05	0.087	0.001
Executive function							
Right prefrontal cortex	0.05	0.052	0.04	0.042	0.07	0.013	0.343
Left prefrontal cortex	0.04	0.058	0.04	0.049	0.05	0.022	0.395
Right temporal cortex	0.03	0.362	0.05	0.097	0.07	0.025	0.765
Right anterior cingulate	0.29	0.198	0.32	0.149	0.44	0.059	0.815
Left cerebellum	0.03	0.197	0.05	0.028	0.06	0.015	0.898

Attention component (ATC). Correlations for the ATC were tested with the anterior and posterior cingulate gyrus, prefrontal cortex, orbitofrontal cortex, BA 25, medial frontal gyrus and the cerebellum bilaterally. In the control group attention was positively correlated with the left anterior cingulate gyrus ($P = 0.039$).

Correlations in the patient group were not significant in any of these regions, and the result of the correlation with the anterior cingulate was significantly different between groups ($P < 0.001$).

Verbal memory component. The regions tested for correlations with the Verbal memory component (VMC) were the hippocampus, anterior cingulate cortex, amygdala, temporal cortex, caudate nucleus, prefrontal cortex and the cerebellum bilaterally.

This component showed significant results in the control group when correlated with the tail of the caudate nucleus in the left hemisphere ($P = 0.023$). Correlation with the left hippocampus came close to significance ($P = 0.084$). The results were significantly different from the patients' correlations in these regions ($P < 0.01$). The VMC was not correlated with any of the selected ROIs in the patient group.

Visual memory component. The Visual memory component (VIMC) was tested for correlations with rCBF in the hippocampus, amygdala, temporal cortex, anterior and posterior cingulate gyrus, angular gyrus, prefrontal cortex and the cerebellum bilaterally.

When correlating visual memory scores with these regions, several significant results were found in the control group. This component was negatively correlated with rCBF in the amygdala in both hemispheres (right, $P = 0.001$ and left, $P = 0.043$), temporal cortex bilaterally (right, $P = 0.031$ and left, $P = 0.066$), right anterior cingulate gyrus ($P = 0.051$), posterior cingulate gyrus (right, $P = 0.047$ and left, $P = 0.064$), and angular gyrus in the right hemisphere ($P = 0.025$). Differences between groups on these correlations were generally not significant. Only the correlation with

the left posterior cingulate region was significantly different in the patient group. The VIMC was not significantly correlated with any of these regions in the patient group.

Language component. This component was correlated with rCBF in the prefrontal cortex, orbitofrontal cortex, medial frontal gyrus, anterior cingulate gyrus, temporal cortex and the cerebellum bilaterally.

In the control group the right prefrontal cortex tended to be positively correlated to Verbal Fluency performance ($P = 0.056$) and was significantly different from the corresponding correlation in the patient group ($P < 0.001$). The patient group correlations were not significant in any region.

The executive component

The selected regions for correlation with the executive component were the prefrontal cortex, orbitofrontal cortex, medial frontal gyrus, anterior cingulate gyrus, temporal cortex and the cerebellum, in both hemispheres.

Controls had positive correlations with the left temporal cortex ($P = 0.056$) and the right cerebellum ($P = 0.007$) in relation to this component, although the results were not significantly different from the patient group. In the patient group, performance was, however, positively correlated with the right temporal cortex ($P = 0.025$), left cerebellum ($P = 0.015$) and the right anterior cingulate gyrus ($P = 0.059$).

Discussion

Control group results

The analyses of rCBF vs. cognitive performance gave several significant correlations in the control group. The main findings for the memory components were correlations with the hippocampus, amygdala, temporal cortex and the posterior cingulate cortex. Language correlated with the prefrontal cortex and general ability with the orbitofrontal cortex and the temporal cortex. The latter region was also associated with executive functions. Activation studies of healthy subjects performing cognitive tasks during PET scanning have shown similar activation sites for the cognitive functions tested in this study [for review see (26)], as for e.g. attention which correlated with the activity in the anterior cingulate gyrus. This is in accordance with numerous activation studies of healthy subjects using tests of attention as activation paradigms, especially tests of selective attention involving response selection or monitoring like the Stroop test (8, 27–30). This test was also one of the tests included in our ATC, where it was highly weighted (score coefficients 0.157–0.181). Therefore, the significant correlation between the attention scores and the anterior cingulate gyrus in the control group seems meaningful.

Patient group results

In general, the correlations found in the control group analysis were not seen in the patient group. A noteworthy result of this study was the fact that cognitive functions of the depressed patients only correlated with rCBF in specific regions of the brain in a few instances; the GAC score significantly correlated with the hippocampus, and the executive component scores with the prefrontal cortex bilaterally, the right temporal cortex and the left cerebellum.

It is interesting that the only tests reaching significant correlations with specific brain regions were those representing normal or near-normal cognitive functions in initial test scores in the patient group (the DART and the WCST error score, $P > 0.05$) (1). The DART constitutes a major part of the weighting in the GAC (coefficient score = 0.388), and the WCST error score was the sole representative in the executive component. Hence, intact cognitive functions can be ascribed to restricted brain regions.

It must be noted that although the general ability and the executive component correlated significantly with specific regions of interest, these regions were not all identical for patients and controls. Both groups correlated with the executive function and the temporal cortex, yet in opposite hemispheres, and the GAC correlated with the hippocampus in the patient group but with the orbitofrontal and the temporal cortex in the control group.

Similar to our study, Awata et al. (15) found no correlations between cognitive function, measured using the MMSE, and rCBF. We were thus not able to replicate two earlier studies in which correlations with cingulate areas and the prefrontal cortex for the memory and ATC were found (14, 31).

Our previous PET study has shown dysfunctional limbic structures in depressed patients (increased blood flow to the hippocampus, the amygdala and the anterior cingulate) (16). Although our patients had severe cognitive dysfunctions in attention as well as in memory, none

of these deficits correlated with the blood flow to the mentioned structures. This may indicate that the cingulate gyrus does not subserve attention in a depressed brain in the same way as in a healthy brain. Our analyses of these patients and controls performing Stroop's test during PET scanning, described in a recent paper, may support this notion (32). Although both groups activated the anterior cingulate gyrus, patients still had very poor performance on the test. The Stroop performance was not correlated with the activity of the PET images as such but with the number of white matter lesions in the patients' brains.

A more complex relationship between cognition and rCBF may apply to the memory and the Verbal Fluency components as well. No correlations were found in the patient group between cognitive dysfunctions within these tasks and any brain region. Similar to the activation study using Stroop's test, we have undertaken a study of these patients performing a Verbal Fluency task during scanning (11). The same conclusion was drawn from this study, i.e. poor cognitive performance cannot be ascribed to proportionally altered neural activity in the implicated brain regions. Hence, we suggest that the lack of correlation between cognition and rCBF may be caused by a disturbance of cerebral circuits and a dysfunctional interaction between the regions of the brain rather than a single dysfunctional region (like the prefrontal cortex) resulting in a cognitive deficit. This is in accordance with the results of a study we performed of the correlational structure of brain regions of the depressed patients compared with matched controls. It is also in agreement with suggestions of Rogers et al. (33) based on an extensive review of evidence from neuropsychological research and neuroimaging of depressed patients. They concluded that depression involves disturbed neural activity rather than reduced activity, and that the abnormalities of brain function may be qualitative, rather than quantitative, in nature.

It may also be that impaired cognition, unlike normal cognition, simply is uncoupled from cerebral blood flow, possibly because it is just more variable.

It cannot be excluded that depressed brains have to compensate for regional dysfunction by recruiting adjacent brain areas as a principle of functional neuroplasticity (34) or by employing compensatory brain areas in response to the reduction of functions in task-related brain areas, also seen in studies of the ageing brain (35). However, as no correlations were found with any other brain regions, the hypothesis of compensatory mechanisms is not exhaustive.

Methodological considerations

There is no ready explanation for the hemispheric differences in the correlation between test scores and the rCBF being negative or positive, e.g. the VIMC was negatively associated with rCBF in the temporal cortex in the right hemisphere but positively correlated with rCBF of the left hemisphere in the control group. Some activation studies have shown that skilled or practised cognitive performance may also be expressed by decreases in blood flow in comparison with unskilled or novel performance (36–38). Hence, the normal and superior cognition represented by the control group may have positive as well as negative associations with the rCBF of the significantly activated regions.

A possible objection to our results could be that the PET images were obtained in a resting state, whereas the neuropsychological data were obtained when actively performing a task. This constitutes two different situations that may be difficult to compare. However, the finding in the control group of associations that seem theoretically reasonable and in accord with a number of activation studies of the cognitive functions involved emphasizes that the method used in our study is meaningful.

The results of the patient group cannot be ascribed to medication as the original test data had ruled out any significant influence of antidepressants.

Although data were adjusted, we did not correct for mass significance because of multiple comparisons in the regression analyses. So far only a few studies have tried to correlate neuropsychological test scores with rCBF. This study allows uncorrected *p*-values to minimize the risk of committing type II errors, and to generate hypotheses on the relationship between cognitive function and brain function for future studies.

Conclusion

The cognitive deficits were not associated with the rCBF of the anatomical structures that, in fact, were affected in our patient group (the hippocampus, DLPFC, orbitofrontal cortex and anterior cingulate cortex). Therefore, our main conclusion is the more general one that disturbed cognitive functions in depression may not relate to specifically located and delimited areas of the brain as normal cognitive functioning seems to do. Intact cognition did correlate with the rCBF of specific brain regions. Obviously our results need replication but, as it stands, our study supports the

demand for more sophisticated theories of the relationship between disturbed cognitive function and the neural substrates of major depression.

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