The Effect of Amphetamine on Regional Cerebral Blood Flow during Cognitive Activation in Schizophrenia

David G. Daniel, Daniel R. Weinberger, Douglas W. Jones, Jeffrey R. Zigun, Richard Coppola, Sharon Handel, Llewellyn B. Bigelow, Terry E. Goldberg, Karen F. Berman, and Joel E. Kleinman

Clinical Brain Disorders Branch, Neurosciences Center at Saint Elizabeths, Intramural Research Program, National Institute of Mental Health, Washington, D.C. 20032

To explore the role of monoamines on cerebral function during specific prefrontal cognitive activation, we conducted a double-blind placebo-controlled crossover study of the effects of 0.25 mg/kg oral dextroamphetamine on regional cerebral blood flow (rCBF) as determined by ^{133}Xe dynamic single-photon emission-computed tomography (SPECT) during performance of the Wisconsin Card Sorting Test (WCST) and a sensorimotor control task. Ten patients with chronic schizophrenia who had been stabilized for at least 6 weeks on 0.4 mg/kg haloperidol participated. Amphetamine produced a modest, nonsignificant, task-independent, global reduction in rCBF. However, the effect of amphetamine on task-dependent activation of rCBF (i.e., WCST minus control task) was striking. Whereas on placebo no significant activation of rCBF was seen during the WCST compared with the control task, on amphetamine significant activation of the left dorsolateral prefrontal cortex (DLPFC) occurred ($p = 0.0006$). Both the mean number of correct responses and the mean conceptual level increased ($p < 0.05$) with amphetamine relative to placebo. In addition, with amphetamine, but not with placebo, a significant correlation ($r = -0.71$; $p < 0.05$) emerged between activation of DLPFC rCBF and performance of the WCST task. These findings are consistent with animal models in which mesocortical catecholaminergic activity modulates and enhances the signal-to-noise ratio of evoked cortical activity.

The results of several studies of regional brain metabolism and blood flow in patients with schizophrenia have suggested physiologic hypoactivity of the prefrontal cortex (PFC) in this disorder (for review, see Weinberger and Berman, 1988). This so-called hypofrontality has been most consistently demonstrated during performance of a behavioral task that appeared to challenge the PFC (Berman et al., 1986; Weinberger et al., 1986a, 1988; Cohen et al., 1987; Volkow et al., 1987; Weinberger and Berman, 1988, for review). Very little is known about the neural mechanisms or potential reversibility of this finding. One possible mechanism that has received increasing attention involves

the function of mesocortical dopaminergic projections. In a study of patients with Parkinson's disease, Weinberger et al. (1986b) observed a negative correlation between the clinical manifestations of central dopaminergic hypoactivity (i.e., rigidity and bradykinesia) and the degree of physiological activation of the PFC during performance of the Wisconsin Card Sort Test (WCST), a cognitive task that relates to dorsolateral prefrontal cortical (DLPFC) function (Milner, 1963; Stuss and Benson, 1983; Stuss et al., 1983). Leenders et al. (1990) have recently reported that the accumulation of L-(^{18}F)-6-fluorodopa in the PFC of patients with Parkinson's disease also correlates with WCST performance. In patients with schizophrenia, Weinberger et al. (1988) recently reported a direct correlation between cerebrospinal fluid (CSF) homovanillic acid (HVA) concentrations and the degree of functional activation of the PFC during performance of the same WCST. These results suggest that cortical dopamine activity may play a role in the cortical manifestations of these pathological conditions. Animal studies support the notion that central catecholaminergic activity affects cortical function. In particular, dopamine has been shown to enhance "signal to noise" by suppressing spontaneous neural activity and enhancing the ability of neural systems to increase neural activity focally in response to a specific stimulus or task (Foote et al., 1975; Sawaguchi, 1987). Conversely, Brozoski et al. (1979) found that depletion of dopamine in a circumscribed area of PFC in rhesus monkeys produced severe impairment in anatomically linked cognitive performance that was reversible with dopamine agonists. Together, these animal and human studies suggest catecholamines are important for the normal modulation of neurophysiological function in the cortex. Their role may be especially relevant for the suppression of random neural activity and enhancement of the capacity to increase neural activity focally in response to a specific environmental stimulus.

A logical next step would be to create a model demonstrating the effects of augmenting catecholaminergic activity on enhancement of signal to noise in humans during performance of a cognitive task linked to a specific brain region. Our observation of an apparent relationship between CSF HVA levels and PFC activation during a prefrontal-linked task hinted at such a possibility and led to the following hypothesis: If physiologic dysfunction of the DLPFC in schizophrenia is related at least in part to deficits in dopamine-mediated mesocortical neural transmission, then a centrally active dopaminergic agonist should increase DLPFC activation during performance of a prefrontal-specific task. If this increase in DLPFC activity reflected an improvement in signal to noise, we would expect to see a phe-

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Correspondence should be addressed to David G. Daniel, M.D., NIMH Neuropsychiatric Research Hospital, William A. White Building, 2700 Martin Luther King, Jr., Avenue, S.E., Washington, DC 20032.

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nomenon analogous to that seen in the animal studies performed by Foote et al. (1975), Johnson et al. (1983), and Sawaguchi (1987). That is, a decrease in background regional cerebral blood flow (rCBF) at baseline and a focal increase in rCBF in the brain regions associated with performance of the task should occur. In order to test this hypothesis, we conducted a preliminary, double-blind placebo-controlled crossover study of the effects of apomorphine, a potent centrally active dopamine receptor agonist (Anden et al., 1967; Ernst, 1967), on DLPFC rCBF during performance of the WCST in eight chronically psychotic patients (Daniel et al., 1989). In each patient with chronic schizophrenia, apomorphine increased the ratio of PFC to non-frontal blood flow during performance of the WCST. In the current study, we have further investigated this hypothesis using amphetamine and a tomographic imaging technique, ^{133}Xe dynamic single-photon emission-computed tomography (SPECT). Amphetamine, with a longer half-life than apomorphine, allowed us to compare directly its effect on the prefrontal-linked cognitive task (WCST) to its effect on a simple control task. SPECT has a number of advantages over 2-D rCBF, including superior resolution, avoidance of superimposition of multiple tissue layers, visualization of subcortical structures, and faster image acquisition.

In order to prevent an amphetamine-induced exacerbation of psychosis, patients in the present study were stabilized on a fixed dose of haloperidol. Haloperidol has a relatively high affinity for blockade of subcortical D₂ receptors (Andersen et al., 1986; Tamminga and Gerlach, 1987), which are thought to be important in mediating psychotic symptoms. In the presence of haloperidol, amphetamine would be expected to stimulate preferentially D₁ receptors, which predominate in the human cortex.

Materials and Methods

Subjects. Ten inpatients from the National Institute of Mental Health research wards of the Neurosciences Center at Saint Elizabeths volunteered and gave informed consent for participation in this study, which had the approval of the institutional review board and radiation safety committee. Each patient fulfilled criteria for chronic schizophrenia (American Psychiatric Association, 1987). Demographic information is summarized in Table 1. Prior to receiving dextroamphetamine, all had been stabilized for at least 6 weeks on a fixed dose of haloperidol. A haloperidol dosage of 0.4 mg/kg/d was used as a target dose subject to the constraints required to attain clinical stabilization. Summarized in Table 2 are mean ratings of negative symptoms, behavioral positive symptoms, and verbal positive symptoms assessed daily by trained nursing staff using the Psychiatric Symptom Assessment Scale (PSAS) for the 2-week period prior to each patient's participation in the study. The PSAS (Bigelow and Berthot, 1989) is a modified version of the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). Symptom ratings range from 0 (not present) to 6 (very severe). Although all of the patients were too ill to live independently in the community, they were clinically stable at the time of the study and able to cooperate with the SPECT and cognitive testing procedures. Diagnoses were made independently by the ward physician and medical director prior to the patients' participation in the study. All patients were free of neurologic or systemic illnesses with implications for cerebral blood flow (e.g., brain injury, hypertension, diabetes, vascular headaches, and hyperlipidemia) and free of alcohol or drug abuse.

^{133}Xe dynamic SPECT technique. In the absence of major cerebral pathology, rCBF directly reflects cerebral metabolism (Raichle et al., 1976; Siesjo, 1984). rCBF was measured with a dedicated-head SPECT system (Tomomatic 564, Medimatic Inc.) using the noninvasive ^{133}Xe inhalation dynamic tomographic imaging procedure (Kanno and Lassen, 1979; Stokely et al., 1980; Celsis et al., 1981; Shirahata et al., 1985). The scanner consists of a rapidly rotating (6 rpm) square array of four detector boxes, each containing 16 NaI scintillation crystals, 25 photomultiplier tubes, and a double-focusing lead collimator (Stokely et al.,

1980). The system is capable of collecting a full set of 80 projections in 5 sec. A high-sensitivity collimator was used to collect five transverse slices simultaneously [16 mm in plane resolution (full-width half-maximum)] of 20-mm thickness, each with centers 20 mm apart. Images were reconstructed using a standard filtered back-projection technique, which includes attenuation and background correction (Stokely et al., 1980; Holm, 1988). rCBF values (ml/min/100 gm) were derived from the sequence of pictures flow algorithm (Kanno and Lassen, 1979; Celsis et al., 1981), which utilizes single-pixel dynamics for flow determination. The 270-sec data acquisition period entailed integration of four data collection periods consisting of a 90-sec uptake collection and three 60-sec washout collections. The input function for the flow algorithm is determined by radioactivity detected by a scintillation probe placed over the right lung, which has been shown to be proportional to arterial blood radioactivity (Holm, 1988).

^{133}Xe dynamic SPECT test conditions. Each patient underwent two sets of rCBF determinations 48–96 hr apart. During the scan procedure, each subject was seated in a semireclined position in a comfortable chair with the head positioned in the scanner. External marker lights were used to center and set the angle of the slices parallel to and at a set distance from the canthomeatal line. The head was immobilized within the gantry using foam-rubber inserts. Each set of rCBF determinations consisted of an initial sham resting procedure done to acclimate the patient to the procedure, followed by two separate rCBF measurements made during performance of two automated cognitive tasks: an automated version of a simple sensorimotor control task (BAR), consisting of matching the geometric orientation of bars, and the prefrontal activation task (WCST). The order of WCST–BAR tasks was counterbalanced across subjects. On each test day, each subject received an oral dose of either placebo or 0.25 mg/kg active dextroamphetamine approximately 120 min prior to rCBF determination. Timing of the administration of amphetamine was based on pharmacokinetic data indicating that plasma levels of 0.25 mg/kg D-amphetamine administered orally peak 2–3 hr after administration (Angrist et al., 1987). The order of active and placebo medication administration also was counterbalanced across subjects. The details of the WCST administration, which requires the patient to create, maintain, and alter abstract sets based on feedback (Grant and Beg, 1948) are described elsewhere (Weinberger et al., 1986a). A computerized version was used that entailed display of choices in a monitor, with responses made by pushing one of four buttons. The BAR and WCST conditions involved similar motoric responses.

Blood pressure was measured immediately after completion of the SPECT procedure on each test day. Respiratory rate and end-expiratory partial pressure of CO₂ (P_{CO₂}) concentration were monitored by continuous capnographic recording during rCBF determinations.

Region of interest analysis. Voxel flow values were displayed on a 32 × 32 matrix employing a 16-color scale. As shown in Figure 1, we selected two SPECT slices oriented parallel to the canthomeatal line for flow analysis. The superior cortical (SC) slice, centered at 60 mm above the canthomeatal line, was selected because it tends to overlap with the DLPFC. The DLPFC is of interest because it has been shown (1) by lesion studies to be associated with performance of the WCST (Milner, 1963; Stuss and Benson, 1983) and (2) to increase rCBF locally in normal controls but not schizophrenic patients during performance of the WCST (Weinberger et al., 1986a, 1988; Berman et al., 1990). As shown in Figure 2, the more inferior slice [referred to as the basal ganglia (BG) slice], centered at 40 mm above the canthomeatal line, included subcortical and more inferior cortical regions including the temporal lobes. The most superior and inferior slices were not analyzed because of apical and airway artifact, respectively.

The procedure by which anatomically based region of interest (ROI) overlays were derived is described in detail elsewhere (Weinberger et al., 1991). In brief, anatomically shaped region of interest overlays were based on earlier high-resolution static SPECT studies of normal controls and validated with comparison to the corresponding magnetic resonance image (MRI) and a standard anatomical atlas (Matsui and Hirano, 1978). Using an elastic adaptation process, these ROIs were individually conformed by computer to the size and shape of the cortical perimeter of each subject in the present study (for details, see Weinberger et al., 1991). In order to remove a possible source of bias in ROI placement, this process was performed prior to flow calculation and was based on an image generated from Xe distribution integrated across all four collections. Visual inspection indicated that the elastic adaptation process appropriately aligned the ROIs with the cortical perimeter.

Table 1. Demographic description of subjects

Patient	Age	Sex	Race ^a	Years of education	Years since first hospitalization
1	22	F	B	12	6
2	45	M	W	16	23
3	29	M	W	9.5	11
4	20	F	W	12	2
5	33	F	W	12	14
6	40	M	W	15	15
7	34	F	W	12.5	11
8	37	M	W	12.5	18
9	21	M	B	8	5
10	35	M	W	13	5
Mean	31.6			12.25	11.0

^a B and W indicate black and white race, respectively.

With a computer, this ROI overlay was then used to generate ROI flow analyses for each of the patients. As indicated in Figure 1, from the SC slice the following cortical ROIs were analyzed for each hemisphere: medial frontal cortex, anterior lateral frontal cortex, dorsolateral frontal cortex, central cortex, temporoparietal cortex, parieto-occipital cortex, occipital cortex, and anterior and posterior cingulate cortex. Also, as shown in Figure 1, for the BG slice, the following ROIs were analyzed for each hemisphere: medial frontal cortex, anterior lateral frontal cortex, dorsolateral frontal cortex, temporofrontal cortex, temporal cortex, temporo-occipital cortex, occipital cortex, caudate, putamen, and thalamus.

Determination of clinical response to treatment. Dichotomous assessment of clinical response (positive responders vs. nonresponders) to amphetamine was performed by consensus of two investigators (L.B.B. and T.E.G.), who were blind to medication condition. Details of the rating procedure and criteria for improvement are detailed elsewhere (Goldberg et al., 1991).

Statistical analysis. All analyses were performed by computer using the Number Cruncher Statistical System, version 5.01 (Hintze, 1987). The control (BAR) and activation (WCST) conditions were analyzed separately.

Absolute rCBF data are affected by variations in cortical arousal, partial pressure of CO₂, and blood volume (Mchenry et al., 1978; Berman and Weinberger, 1986; Mathew et al., 1986). Our design, in which each patient serves as his or her own control, tends to minimize the effect of interindividual variation in these variables. On our comparisons of rCBF across conditions, we used a two-tailed matched-pairs *t*-test statistical analysis in which each patient served as his or her own control.

Initially, we examined the effects of amphetamine on rCBF during the BAR task and subsequently during the WCST task, using two-tailed matched-pairs *t* tests to compare placebo and active conditions. The effects of amphetamine were examined separately for each individual ROI and for mean cortical and subcortical rCBF in each slice.

Next, we looked at the effect of amphetamine on activation of rCBF over baseline (change score analysis; Berman et al., 1986, 1988; Weinberger et al., 1986a, 1988). Change score analysis uses the BAR condition as a control for the nonprefrontal, nonspecific physiologic components of the WCST condition (i.e., arousal, visual stimulation and eye scanning, button pushing, etc.). Thus, this analysis has the potential to detect very subtle effects with a high ratio of signal to noise. Change scores were derived by subtracting the flow for a given ROI during the WCST condition from the flow for that ROI during the BAR condition for each subject. For example, the change score for the dorsolateral frontal cortex was defined by [dorsolateral frontal flow (ml/mg/min) during the WCST condition] minus [dorsolateral frontal flow (ml/mg/min) during the BAR condition]. Change scores were calculated separately for the placebo and active conditions. In each case, the WCST and BAR conditions were compared using matched-pairs *t* tests. In order to assess the effect of amphetamine, the change scores for the amphetamine and placebo conditions were compared with two-tailed matched-pairs *t* tests.

Thus, rCBF was evaluated across five conditions: amphetamine versus placebo on the BAR task, amphetamine versus placebo on the WCST, BAR versus WCST on placebo, BAR versus WCST on amphetamine, and WCST-BAR on placebo versus WCST-BAR on amphetamine.

The extent to which clinical responders and nonresponders to am-

Table 2. Clinical descriptions

Patient	Mean prestudy PSAS symptom ratings ^a			Clinical improvement on amphetamine
	Behavioral positive	Verbal positive	Negative	
1	2.4	1.7	1.5	no
2	1.3	0.57	2.1	yes
3	0.26	0.06	0.46	yes
4	1.1	0.87	0.60	no
5	1.7	0.75	0.90	no
6	1.0	0.48	0.96	no
7	0.75	0.34	1.3	yes
8	0.48	0.29	1.1	no
9	0.82	0.30	1.8	no
10	1.2	0.89	0.83	no
Mean	1.1	0.63	1.2	

^a Values are means of daily ratings for 2 weeks prior to study.

Figure 1. These BG and SC slices are 2 cm thick and centered at 40 mm and 60 mm, respectively, above the canthomeatal line. ROIs for the SC slice (*left*) include 1, medial frontal cortex; 2, anterior lateral frontal cortex; 3, dorsolateral frontal cortex; 4, central cortex; 5, temporoparietal cortex; 6, parieto-occipital cortex; 7, occipital cortex; 8, anterior cingulate cortex; and 9, posterior cingulate cortex. ROIs for the BG slice (*right*) include 1, insular cortex; 2, caudate; 3, putamen; 4, thalamus; 5, medial frontal cortex; 6, anterior lateral frontal cortex; 7, dorsolateral frontal cortex; 8, temporo-frontal cortex; 9, temporal cortex; 10, temporo-occipital cortex; and 11, occipital cortex. *L*, left; *R*, right.

phetamine differed in the effect of amphetamine on (1) activation of DLPFC rCBF (WCST-BAR on placebo vs. WCST-BAR on amphetamine) and (2) WCST performance (on placebo vs. on amphetamine) was assessed using two-sample *t* tests.

The extent to which mean daily PSAS ratings of behavioral positive, verbal positive, and negative symptoms for 2 weeks prior to the study predicted the effect of amphetamine on (1) activation of DLPFC rCBF and (2) WCST performance was assessed using the Spearman rank-order coefficient.

Serum amphetamine levels were measured using a high-pressure liquid chromatography analysis with a sensitivity of 10 ng/ml. The mean time that elapsed between oral administration of amphetamine and drawing of serum amphetamine levels was 60.6 min. The extent to which serum amphetamine levels were predictive of rCBF and WCST performance was examined using the Spearman rank-order coefficient.

Blood pressure and partial pressure of CO₂ (P_{CO₂}) were examined

across each of the above conditions with two-tailed matched-pairs *t* tests.

Results

As seen in Table 3, the effect of amphetamine during the BAR control task was to produce a modest, statistically nonsignificant, global reduction of flow. As seen in Table 4, amphetamine had a similar effect on rCBF during the WCST.

Change score analysis

Figure 2 illustrates cortical activation of rCBF over baseline (WCST-BAR) by region and medication in the SC slice. In the placebo condition, a diffuse, unfocused activation over baseline

Figure 2. Activation over baseline (WCST-BAR) by region during the placebo (*top*) and amphetamine states (*bottom*) in the SC slice. The height of each bar indicates the difference in rCBF (ml/100 gm/min) between the WCST and BAR conditions for each region. SE is indicated by the vertical lines; *N* = 10 both placebo and amphetamine conditions. ROIs shown include medial frontal cortex (MF), anterior lateral frontal cortex (ALF), dorsolateral frontal cortex (DLF), central cortex (C), temporoparietal cortex (TP), parieto-occipital cortex (PO), occipital cortex (O), anterior cingulate cortex (AC), and posterior cingulate cortex (PC). All *P* values refer to paired *t* tests comparing rCBF during the WCST and BAR conditions. All *P* values were >0.05 except as follows: *left* DLF: paired *t* = 5.10, SE = 0.84, *P* = 0.0006; *right* O: paired *t* = 2.78, SE = 1.4, *P* < 0.03; AC: *t* = 3.2, SE = 0.98, *P* < 0.02.

Table 3. Effect of amphetamine on rCBF during BAR control task

Region ^a	Slice ^b	rCBF ^c		<i>t</i> ^d	SE ^e	<i>P</i>
		Placebo	Amphetamine			
Left cortex	3	62.3	59.7	1.18	2.2	0.27
Right cortex	3	62.9	60.3	1.09	2.3	0.30
Left cortex	2	63.2	60.9	1.03	2.2	0.33
Right cortex	2	63.6	61.6	0.84	2.4	0.42
Left subcortex	2	62.5	62.1	0.17	2.4	0.87
Right subcortex	2	62.9	61.1	0.79	2.3	0.45

^a Calculated by averaging the mean rCBF of all individual ROIs contained within the area described.

^b Slices 2 and 3 were centered at 40 and 60 mm above the canthomeatal line, respectively.

^c Values are mean flow expressed in ml/100 gm/min.

^d Matched-pairs *t* tests; *n* = 10.

^e Standard error of difference.

was seen throughout the cortex. It was not statistically significant in any of the individual ROIs or in the cortex of either hemisphere. SEs were generally relatively large, suggestive of substantial variation in response among the subjects. In marked contrast to the placebo condition, activation over baseline in the amphetamine condition indicated a relatively focused, regionally specific activation in the left lateral frontal regions, which reached statistical significance only in the DLPFC ($p = 0.0006$). Suppression of activation was seen elsewhere in the left cortex. Activation did not reach statistical significance in any of the other left cortical ROIs or in either hemispheric cortical mean for the SC slice. In the right hemisphere, activation of the occipital and anterior cingulate cortices reached statistical significance at the 0.05 level. A direct comparison of differences in change scores in the DLPFC on amphetamine did not reach significance.

In the BG slice, for both the amphetamine and placebo conditions, activation of rCBF over baseline (WCST–BAR) did not reach statistical significance in any of individual ROIs or in the subcortical or cortical means of either hemisphere. There were no significant differences in regional activation (WCST–BAR) between the amphetamine and placebo conditions.

Serum amphetamine assay

Serum levels of amphetamine ranged from 18 to 82 ng/ml (mean, 38.6 ng/ml). Serum amphetamine levels did not significantly correlate with rCBF during the BAR task or the WCST, or with

the change scores between the BAR and WCST conditions in any ROI or in any hemisphere. Serum amphetamine levels also did not correlate significantly with cognitive change scores on the WCST.

Autonomic variables

Amphetamine caused a modest, nonsignificant increase in mean systolic blood pressure [120.7 and 125.2 mm Hg during the placebo and amphetamine conditions, respectively ($t = 0.88$; $p = 0.40$)]. Because of technical difficulties, information on P_{CO_2} was only available for seven subjects. Mean P_{CO_2} during uptake is described in Table 5 for each of the four test conditions. There were no significant differences in mean P_{CO_2} during either uptake or washout (not shown) across either task or drug condition.

WCST performance

As seen in Table 6, amphetamine had a small but significant effect on two parameters of performance on the WCST, number of correct responses, and percent conceptual level responses. The latter describes the percentage of all responses that fall within a string of at least three correct responses. Further details of test performance are elaborated elsewhere (Goldberg et al., 1991).

On placebo, there was no significant correlation between rCBF in the DLPFC and any measure of performance. As shown in Figure 3, on amphetamine, a statistically significant correlation

Table 4. Effect of amphetamine on rCBF during WCST task

Region ^a	Slice ^b	rCBF ^c		<i>t</i> ^d	SE ^e	<i>P</i>
		Placebo	Amphetamine			
Left cortex	3	65.0	61.5	1.65	2.1	0.13
Right cortex	3	65.6	62.2	1.74	2.0	0.12
Left cortex	2	65.1	62.8	1.38	1.6	0.20
Right cortex	2	65.8	63.8	1.28	1.6	0.23
Left subcortex	2	64.2	62.7	0.77	1.9	0.46
Right subcortex	2	64.2	62.7	0.77	2.0	0.46

^a Calculated by averaging the mean rCBF of all individual ROIs contained within the region described.

^b Slices 2 and 3 were centered at 40 and 60 mm above the canthomeatal line, respectively.

^c Values are mean flow expressed in ml/100 gm/min.

^d Matched-pairs *t* tests; *n* = 10.

^e Standard error of difference.

Table 5. P_{CO_2} by task and by drug condition

	P_{CO_2} ^a				t^b	SE ^c	P
	Amphetamine	Placebo	WCST	BAR			
Task							
WCST	42.1	40.3	—	—	0.97	1.9	0.37
BAR	41.9	40.3	—	—	0.75	2.1	0.48
Drug							
Amphetamine	—	—	42.1	41.9	0.47	0.61	0.65
Placebo	—	—	40.3	40.3	0	0.22	1.0

^a Mean P_{CO_2} during 90-sec ^{133}Xe uptake phase.^b Matched-pairs t tests; $n = 7$.^c Standard error of difference.

emerged between left DLPFC rCBF activation (WCST–BAR) and failures to maintain set ($\rho = -0.71$; $p < 0.05$).

Clinical variables

Clinical changes resulting from amphetamine were highly variable and generally mild, ranging from increased cooperativeness, optimism, and improved mood to irritability and dysphoria. Three patients were felt to have shown clinically significant improvement, whereas one patient significantly deteriorated. Clinical response is described in Table 2 and is further detailed elsewhere (Goldberg et al., 1991).

In the patients who were judged positive clinical responders to amphetamine, compared to those who were judged nonresponders, there was no significant difference in the effect of amphetamine on (1) DLPFC rCBF activation (WCST–BAR) or (2) any measure of WCST performance. There was no significant correlation between mean daily PSAS ratings of verbal positive, behavioral positive, and negative symptoms for 2 weeks prior to the study and the effect of amphetamine on (1) DLPFC rCBF activation (WCST–BAR) or (2) either of the two measures of WCST performance that improved with amphetamine (number of correct responses and percent conceptual level).

Discussion

The chief finding of this study is that, in patients with schizophrenia, amphetamine appears to enhance the ability of the cortex to focus activity in response to a regionally processed cognitive task (WCST). Amphetamine produced a nonsignificant trend toward a diffuse reduction of rCBF that was independent of task. This result is consistent with earlier studies (Abreu et al., 1949; Mathew and Wilson, 1985; Wolkin et al., 1987; Kahn et al., 1989). On placebo, no significant activation

of rCBF was seen during the WCST compared with the control task. On amphetamine, significant task-specific activation of the left DLPFC occurred. As expected, the DLPFC activation produced by the WCST was predominantly left sided, a laterality pattern that is consistent with earlier data describing laterality patterns of rCBF during performance of the WCST (Berman and Weinberger, 1990a) and consistent with the laterality effects of cerebral lesions on organization and planning of responses, particularly in regard to sorting performance (for review, see Mcfie and Piercy, 1952; Milner, 1963; Petrides and Milner, 1982). Elsewhere in the cortex as well as subcortically, activation over baseline (WCST–BAR) appears to have been suppressed by amphetamine. The effects of amphetamine on rCBF were accompanied by a modest but statistically significant improvement on two measures of performance on the prefrontal-linked task (WCST). Moreover, on amphetamine, but not on placebo, a significant correlation emerged between activation of DLPFC rCBF and one measure of performance on the WCST, namely, loss of set. Overall, the results support the hypothesis that dysfunction in mesocortical monoaminergic activity is related to “hypofrontality” in schizophrenia, and suggest that such deficits are, in part, reversible. These findings may also represent a human equivalent of animal data (Foote et al., 1975; Sawaguchi, 1987), in which catecholamines enhance evoked activity (signal) and suppress spontaneous (noise) neurophysiological activity in the cortex.

Amphetamine effects on cortical activity

In animals, acute parenteral amphetamine administration has usually produced diffuse increases in cerebral blood flow and metabolism (Nahorski and Rogers, 1973; Carlsson et al., 1975; Berntman et al., 1976, 1978; McCulloch and Harper, 1977;

Table 6. Effect of amphetamine on WCST task performance

Measure	Placebo	Amphetamine	t^a	SE ^b	P	N
Number of correct responses	72	84	2.52	4.7	0.036	9
Percent conceptual level	44.7	54.6	2.51	3.9	0.036	9
Number of categories correctly completed	3.1	3.8	1.41	0.50	0.19	10
Failures to maintain set	2.33	2.22	0.36	0.31	0.73	9
Percent perseverative error	19.6	18.7	0.20	4.3	0.85	9

^a Matched-pairs t tests.^b Standard error of difference.

Figure 3. The relationship between activation of rCBF over baseline (WCS-BAR) and WCS performance. Spearman's rank order coefficient is shown (placebo condition: $n = 10$, $\rho = -0.13$, $P = \text{NS}$; amphetamine condition: $n = 9$, $\rho = -0.71$, $P < 0.05$).

Neuser and Hoffmeister, 1977; Wechsler et al., 1979; Porrino et al., 1983). However, other animal studies utilizing sensory and/or behavioral activation paradigms suggest that dopamine and norepinephrine may suppress spontaneous neural firing while specifically enhancing the capacity of neural systems to increase activity focally in response to a specific stimulus or task (Foote et al., 1975; Johnson et al., 1983; Sawaguchi, 1987). For example, Foote and co-workers (Foote et al., 1975) demonstrated that, in the auditory cortex of conscious squirrel monkeys, microiontophoretically applied norepinephrine preferentially reduced spontaneous activity relative to evoked response to vocalizations, enhancing the difference between background and stimulus-bound activity. Johnson and co-workers (Johnson et al., 1983) demonstrated that dopamine locally applied to the caudate inhibited spontaneous activity, but actually facilitated evoked activity. In conscious monkeys, Sawaguchi (1987) studied the effect of infusing dopamine and norepinephrine through a cannula into the PFC during different phases of a visual attention task. He found that certain neurons only responded to dopamine, and others only to norepinephrine, during specific phases of the task, and while the firing rate of these neurons was increased, background activity was suppressed. These and other animal studies (Bunney et al., 1987; Robins and Everitt, 1987) suggest that catecholamines are modulating the ratio of signal to noise.

No adequate human model has demonstrated a comparable effect of catecholamines on signal-to-noise modulation in humans. However, a number of authors have studied the effects of amphetamine on resting rCBF and metabolism in human subjects. The trend in most of the studies was toward a modest, often statistically nonsignificant, global decrease in cerebral blood flow or metabolism similar to that we observed (Abreu et al.,

1949; Mathew and Wilson, 1985; Wolkin et al., 1987; Kahn et al., 1989). Exceptions included studies of two stuporous postcraniotomy patients in whom no changes were seen (Shenkin, 1951) and of an amphetamine addict who had taken an unknown dose (Berglund and Risberg, 1980). The trend toward a global decrease in flow, while apparently consistent with the aforementioned animal studies, contrasts with the other animal work in which evidence was found of diffuse increases in cerebral blood flow and metabolism in response to acute doses of amphetamine (Nahorski and Rogers, 1973; Carlsson et al., 1975; Berntman et al., 1976, 1978; McCulloch and Harper, 1977; Neuser and Hoffmeister, 1977; Wechsler et al., 1979; Porrino et al., 1983). The apparent contrast in findings may in part be attributable to the much higher dosages and more invasive measurement techniques used in some of the animal studies, and to the presence or absence of cerebral activation paradigms. The importance of the activation paradigm variable in humans is illustrated by the present study where the modest nonsignificant effects of amphetamine in reducing mean cortical rCBF during both the BAR and WCS tasks contrasted strikingly with amphetamine's effects on activation. If we had not employed an activation-baseline protocol, we would have concluded, as have others, that the only effect of amphetamine on human brain activity was a modest global diminution.

Amphetamine effects on neural transmission

Substantial uncertainty exists regarding the specificity, location, and mechanism of amphetamine's effect on neural transmission. Delineation of the precise neurotransmitter responsible for amphetamine's effects in the present study is complicated by the nonspecificity of amphetamine's effects on monoaminergic activity, including but not limited to the release of dopamine,

norepinephrine, and 5-HT from their storage sites in nerve terminals (Weiner, 1972, 1980; Moore, 1978; Creese, 1983; Kuczenski, 1983, 1989; Glennon et al., 1987). It could be argued that the effects seen of amphetamine and apomorphine on rCBF were a result of direct vasoactive effects on vasculature. Dopaminergic, serotonergic, and β_1 , α_1 , and α_2 adrenergic influences on vasoactive receptors have been identified in human and animal cerebral vessels (Jauzac et al., 1982; Marin and Rivilla, 1982; McCulloch, 1984; Leenders et al., 1985; Nakai et al., 1986, for review). However, in both our earlier study of apomorphine (Daniel et al., 1989) and the present study of amphetamine, effects on *global* flow were not statistically significant. In contrast, apomorphine changed the blood flow *pattern*, increasing rCBF significantly in the PFC relative to the nonfrontal areas (Daniel et al., 1989). This is in contrast to the global changes in flow that would have been more consistent with a direct vasodilatory effect. In the present study, amphetamine significantly *increased* left DLPFC rCBF activation while *reducing* mean flow in the cortex, again inconsistent with a diffuse vasoactive effect. Moreover, a diffuse vasoactive effect would not have been expected to exert the *task-specific* activation of rCBF as was seen in the present study. The possibility that a diffuse vasoactive effect explains the findings of the present study would also be inconsistent with the data suggesting that amphetamine produces diffuse decreases in cerebral glucose metabolism as measured by the deoxyglucose method (Wolkin et al., 1987), which is relatively insensitive to changes in CBF (Sokoloff, 1984). Studies in the rat provide still further evidence that changes in local cerebral glucose metabolism, rather than direct dopaminergic effects on brain vasculature, are responsible for changes in rCBF that occur after dopaminergic stimulation (Beck et al., 1987). The possibility that the results of this study represent chance findings emerging because of multiple *t* tests is also unlikely considering the prior human research implicating DLPFC in the processing of the WCST.

In human subjects, Guell and associates (Guell et al., 1982) found that 0.2 mg/kg pibedil produced a 22% global, homogeneous increase in rCBF. In a resting non-placebo-controlled ^{133}Xe inhalation rCBF study of 10 drug-free patients with schizophrenia selected for "hypofrontality," pibedil (0.1 mg/kg, i.v.) restored near-normal frontal blood flow (Geraud et al., 1987). These studies, in which relatively specific dopamine agonists increased global or frontal blood flow in human subjects at rest, contrast with the global reductions in blood flow observed in human subjects at rest with amphetamine and raise the possibility of a differential effect of dopamine and norepinephrine. On this basis, it could be argued that the modest, nonspecific global CBF-reducing effects of amphetamine are due to its noradrenergic actions, and that the regionally and task-specific activating effects are due to its dopaminergic actions. Consistent with this interpretation, our earlier investigation of apomorphine (Daniel et al., 1989), carried out during performance of the WCST, produced an increase in the ratio of prefrontal to nonfrontal rCBF. Both dopamine and norepinephrine have been shown to facilitate evoked neuronal activity while suppressing background activity (Foote et al., 1975; Sawaguchi, 1987), and a substantial body of work suggests a functional interaction among the noradrenergic and dopaminergic systems in modulating cerebral function (Antelman and Caggiula, 1977; Tassin et al., 1982, 1986). This was incisively demonstrated by Sawaguchi's (1987) finding that locally applied norepinephrine and dopamine in the monkey PFC produced discrete signal-to-noise-

enhancing functions during different phases of the same task. If we apply this scenario to the present study, norepinephrine could be seen as inducing a state of anticipation or readiness manifested physiologically by a global reduction in blood flow, whereas dopamine would act on this physiologically primed substrate to produce an anatomically and task-specific physiological response to the DLPFC-linked task.

A potential role for the 5-hydroxyindole acetic acid (5-HIAA)-enhancing effects of amphetamine (Weiner, 1972) in modulation of PFC function must also be considered in light of (1) the existence of serotonergic neuron projections to the PFC (Jacobs et al., 1984; Lindvall and Bjorklund, 1984; Vanderwolf, 1987) and (2) a previously observed significant correlation between CSF 5-HIAA and relative PFC rCBF during performance of the WCST (Weinberger et al., 1988). On the other hand, a study of prefrontal cognitive function in rhesus monkeys after prefrontal 5-HT depletion revealed no impairment (Brozoski et al., 1979).

Amphetamine and schizophrenia

Several methodological issues should be addressed in interpreting the effects of amphetamine in a schizophrenic patient population. One factor obscuring interpretation of the results was the necessity of stabilizing schizophrenic patients on haloperidol prior to the study in order to prevent potential exacerbation of psychotic symptoms by amphetamine. Haloperidol was selected because of its relative selectivity for D_2 receptors relative to D_1 receptors (for review, see Andersen et al., 1986; Tamminga and Gerlach, 1987). The latter predominate in the cortex (Savasta et al., 1986). It is doubtful that haloperidol played a significant role in the activation deficits observed in the schizophrenic patients because deficits in PFC metabolism have also been reported in never-medicated schizophrenic patients (Chabrol et al., 1986) as well as schizophrenic patients who had been drug-free for several weeks (Weinberger et al., 1986a, 1988; Geraud et al., 1987). Furthermore, Berman et al. (1986) reported qualitatively identical deficits in PFC activation during performance of the WCST in both neuroleptic-treated and drug-free schizophrenic patients. It is also unlikely that haloperidol is a factor in the WCST-related activation effect of amphetamine, because haloperidol's effects should not be behavior specific.

It could be argued that the enhancement in test results and the DLPFC activation seen in the present study were secondary to a regionally and task-independent nonspecific alerting effect. However, in a larger group of patients with schizophrenia that included the present sample, amphetamine did not produce improvement in performance of tests of vigilance and attention, or of memory (Goldberg et al., 1991). The previously described evidence for a link between PFC function in schizophrenia and deficits in central dopaminergic activity (Weinberger et al., 1988; Daniel et al., 1989) is a more tenable explanation for the apparent specificity of amphetamine's effect on performance of a DLPFC-linked task in schizophrenic patients. Of interest would be future studies of the effect, if any, of amphetamine on WCST performance and DLPFC activation in normal controls with intact mesocortical dopamine systems.

The concept of exogenous dopaminergic agents enhancing and modulating PFC activity in schizophrenia is not easily reconciled with the dopamine hypothesis of schizophrenia, which attributes psychotic symptoms to dopamine hyperactivity. For example, a number of studies suggest that amphetamine may

induce psychotic states that in some respects resemble schizophrenia (Connell, 1958; Ellinwood, 1967; Angrist and Gershon, 1970; Snyder, 1977) and worsen psychotic symptoms in patients with preexisting schizophrenia (Casey et al., 1961; Chiarello and Cole, 1987, for review). Paradoxically, however, there have been reports of efficacy of centrally active dopamine agonists in alleviating both positive symptoms (i.e., hallucinations, excitement, delusions) and, to a greater extent, so-called negative or defect symptoms (i.e., emotional blunting, anergy, anhedonia, amotivation, social withdrawal) in schizophrenia (Inanaga et al., 1972, 1975; Buchanan et al., 1975; Gerlach and Lohdort, 1975; Ogura et al., 1976; Brambilla et al., 1979; Alpert and Rush, 1983; Kay et al., 1985–86; Opler et al., 1985). In the present study, patients with schizophrenia were treated simultaneously with (1) an antipsychotic (i.e., haloperidol) that has a relatively high affinity for blockade of subcortical D_2 receptors (Andersen et al., 1986; Tamminga and Gerlach, 1987), which are thought to be important in mediating positive psychotic symptoms, and (2) amphetamine, which in the presence of haloperidol would be expected to stimulate preferentially D_1 receptors. Because D_1 receptors predominate in the cortex, haloperidol should have relatively little effect on amphetamine's action on the cortex. This scenario appears to have been successful in that in the present study PFC function was enhanced, while clinically significant adverse psychiatric effects were minimal (Goldberg et al., 1991).

Conclusions based on this study should be considered tentative because of the relatively modest sample size and uncertainty about the location, mechanism, and specificity of amphetamine's effect on neural transmission. Nevertheless, in a placebo-controlled randomized crossover double-blind design in which each patient served as his or her own control, amphetamine with regional and task specificity significantly increased DLPFC activation during performance of a PFC-linked cognitive task despite its globally reducing rCBF. The clinical concomitants of these physiological phenomena were a modest improvement in performance on the task and the emergence of a significant correlation between one aspect of performance and activation of DLPFC rCBF. The results are consistent with animal studies suggestive of a role for catecholamines in modulating and enhancing the signal-to-noise ratio of cortical activity, and suggest that in schizophrenia deficits in PFC function are, in part, reversible.

References

- Abreu BE, Liddle GW, Burks AL, Sutherland V, Elliot HW, Simon A, Margolis L (1949) Influence of amphetamine sulfate on cerebral metabolism and blood flow in man. *J Am Pharmacol Assoc* 38:186–188.
- Alpert M, Rush M (1983) Comparison of the effects of Parkinson's disease in schizophrenia. *Psychopharmacol Bull* 196:118–120.
- American Psychiatric Association (1987) Diagnostic and statistical manual for statistical disorders, 3rd ed, rev, pp 187–198. Washington, DC: American Psychiatric Association.
- Anden NE, Rubenson A, Fuxe K (1967) Evidence for dopamine receptor stimulation by apomorphine. *J Pharm Pharmacol* 19:627–629.
- Andersen PH, Nielsen EB, Gronvald FC, Braestrup C (1986) Some atypical neuroleptics inhibit (3H) SCH 23390 binding *in vivo*. *Eur J Pharmacol* 120:143–144.
- Angrist B, Corwin J, Bartlett B, Cooper T (1987) Early pharmacokinetics and clinical effects of oral D -amphetamine in normal subjects. *Biol Psychiatry* 22:1357–1368.
- Angrist BM, Gershon S (1970) The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. *Biol Psychiatry* 2:95–107.
- Antelman SM, Caggiula AR (1977) Norepinephrine-dopamine interactions and behavior. *Science* 195:646–653.
- Beck T, Moller H, Nowak K, Kriegstein J, Kuschinsky K (1987) Alterations in regional energy metabolism in rat brain produced by small and large doses of apomorphine. *Eur J Pharmacol* 139:139–146.
- Berglund M, Risberg J (1980) Regional cerebral blood flow in a case of amphetamine intoxication. *Psychopharmacology* 70:219–221.
- Berman KF, Weinberger DR (1986) Cerebral blood flow studies in schizophrenia. In: *Handbook of schizophrenia* (Nasarallah HA, Weinberger DR, eds), pp 277–308. New York: Elsevier.
- Berman KF, Weinberger DR (1990a) Lateralization of cortical function during cognitive tasks: regional cerebral blood flow studies of normal individuals and patients with schizophrenia. *J Neurol Neurosurg Psychiatry* 53:150–160.
- Berman KF, Weinberger DR (1990b) The relationship between “frontal” function in patients with Parkinson's disease and brain dopaminergic activity as measured by PET. *Neurology [Suppl]* 40:168.
- Berman KF, Zec RF, Weinberger DR (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention and mental effort. *Arch Gen Psychiatry* 43:126–135.
- Berman KF, Illowsky BP, Weinberger DR (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity. *Arch Gen Psychiatry* 45:616–622.
- Berman KF, Gold J, Randolph C, Jones DW, Berg GW, Goldberg TE, Carson RE, Weinberger DR (1990) Studies of frontal lobe function with positron emission tomography and regional cerebral blood flow. *J Nucl Med [Suppl]* 40:750.
- Berntman L, Carlsson C, Hagerdal N, Siesjo BK (1976) Excessive increase in oxygen uptake and blood flow in the brain during amphetamine intoxication. *Acta Physiol Scand* 97:264–266.
- Berntman L, Carlsson C, Hagerdal N, Siesjo BK (1978) Circulatory and metabolic effects in the brain induced by amphetamine sulfate. *Acta Physiol Scand* 102:310–323.
- Bigelow LB, Berthot BD (1989) The Psychiatric Symptom Assessment Scale (PSAS). *Psychopharmacol Bull* 25:168–179.
- Brambilla F, Scarone S, Ponzano M, Maffei C, Nobile P, Rovere C, Guastella A (1979) Catecholaminergic drugs in chronic schizophrenia. *Neuropsychobiology* 5:185–200.
- Brozoski TJ, Brown RN, Rosvold HE, Goldman PS (1979) Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science* 31:929–932.
- Buchanan FH, Parton RV, Warren JW, Baker EP (1975) Double blind trial of L-dopa in chronic schizophrenia. *Aust NZ J Psychiatry* 9:269.
- Bunney BS, Sesak SR, Silver NL (1987) Mid brain dopaminergic systems: neurophysiology and electrophysiological pharmacology. In: *Psychopharmacology: the third generation of progress* (Meltzer HY, ed), pp 113–126. New York: Raven.
- Carlsson C, Hagerdal N, Siesjo BK (1975) Influence of amphetamine sulfate on cerebral blood flow and metabolism. *Acta Physiol Scand* 94:128–129.
- Casey JF, Hollister LE, Klett CJ, Lasky JJ, Caffey EM (1961) Combined drug therapy of chronic schizophrenia. *Am J Psychiatry* 117:997–1003.
- Celsis P, Goldman T, Henriksen L, Lassen NA (1981) A method of calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 5:641–645.
- Chabrol H, Guell A, Bes A, Morn P (1986) Cerebral blood flow in schizophrenic adolescents. *Am J Psychiatry* 143:130.
- Chiarello RJ, Cole JE (1987) The use of psychostimulants in general psychiatry. *Arch Gen Psychiatry* 44:286–295.
- Cohen RM, Semple WE, Gross M, Nordahl TE, DeLisi LE, Holcomb HH, King AC, Morihisa JM, Pickar D (1987) Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sci* 40:2031–2039.
- Connell PH (1958) Maudsley monograph No 5, Amphetamine psychosis. London: Oxford UP.
- Creese I (1983) Stimulants: neurochemical, behavioral, and clinical perspectives. New York: Raven.
- Daniel DG, Berman KF, Weinberger DR (1989) The effect of apomorphine on regional cerebral blood flow in schizophrenia. *J Neuropsychiatry* 1:377–384.

- Ellinwood EH (1967) Amphetamine psychosis: I. A description of the individuals and process. *J Nerv Ment Dis* 144:273–283.
- Ernst AM (1967) Mode of action of apomorphine and dextroamphetamine on gnawing compulsion in rats. *Psychopharmacology (Berlin)* 10:316–323.
- Foot SL, Freedman R, Oliver PA (1975) Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. *Brain Res* 86:229–242.
- Geraud G, Arne-Bes MC, Guell A, Bes A (1987) Reversibility of hemodynamic hypofrontality in schizophrenia. *J Cereb Blood Flow Metab* 7:9–12.
- Gerlach J, Lohdort K (1975) The effect of L-dopa on young patients with simple schizophrenia treated with neuroleptic drugs. *Psychopharmacology (Berlin)* 44:105–110.
- Glennon RA, Yousif M, Naiman N, Kalix P (1987) Methcathinone: a new and potent amphetamine-like agent. *Pharmacol Biochem Behav* 26:547–551.
- Goldberg TE, Bigelow LB, Weinberger DR, Daniel DG, Kleinman JE (1991) Cognitive and behavioral effects of the co-administration of dextroamphetamine and haloperidol in schizophrenia. *Am J Psychiatry* 148:78–84.
- Grant AD, Beg EA (1948) A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Wiegand-type card sorting problem. *J Exp Psychol* 38:404–411.
- Guell A, Geraud G, Jauzac PH, Victor G, Arne-Bes MC (1982) Effects of a dopaminergic agonist (piribedil) on cerebral blood flow in a man. *J Cereb Blood Flow Metab* 2:255–257.
- Hintze JL (1987) Number cruncher statistical system: version 5.01. Kaysville, UT: Jerry L. Hintze.
- Holm S (1988) Dynamic single photon emission computerized tomography of the human brain for measurement of regional cerebral blood flow: a critical reappraisal. Copenhagen: H. C. Orsted Institute.
- Inanaga K, Inoue K, Tachibana H, Oshima M, Kotorii T (1972) Effect of L-dopa in schizophrenia. *Folia Psychiatr Neurol Jpn* 26:145–157.
- Inanaga K, Nakazawa Y, Inoue K, Tachibana H, Oshima M (1985) Double blind controlled study of L-dopa therapy in schizophrenia. *Folia Psychiatr Neurol Jpn* 29:123–143.
- Jacobs BL, Heym J, Steinfels GF (1984) Physiological and behavioral analysis of raphe unit activity. In: *Handbook of psychopharmacology: drugs, neurotransmitters, and behavior*, Vol 18 (Iversen LL, Iversen SD, Snyder SH, eds), pp 343–395. New York: Pergamon.
- Jauzac P, Blasco A, Vigoni P, Valdivie P, Bes A (1982) Cerebral circulatory effects of a dopaminergic agonist (apomorphine) in the dog. *J Cereb Blood Flow Metab* 2:369–372.
- Johnson SW, Palmer MR, Freedman R (1983) Effects of dopamine on spontaneous and evoked activity of caudate neurons. *Neuropharmacology* 22:843–851.
- Kahn DA, Prohovnik I, Lucas R, Sackeim HA (1989) Dissociated effects of amphetamine on arousal and cortical blood flow in humans. *Biol Psychiatry* 25:755–767.
- Kanno I, Lassen NA (1979) Two methods of calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 3:71–76.
- Kay SR, Opler LA (1985–86) L-Dopa in the treatment of negative schizophrenic symptoms: a single subject experimental study. *Int J Psychiatry Med* 15:293–298.
- Kuczenski R (1983) Biochemical actions of amphetamine and other stimulants. In: *Stimulants: neurochemical, behavioral, and clinical perspectives* (Creese I, ed), pp 31–61. New York: Raven.
- Kuczenski R (1989) Concomitant characterization of behavioral and striatal monoamine response to amphetamine using *in vivo* microdialysis. *J Neurosci* 9:2051–2065.
- Leenders KL, Wolfson L, Gibbs JM, Wise RJS, Causton R, Jones T, Legg NJ (1985) The effects of L-dopa on regional cerebral blood flow in oxygen metabolism in patients with Parkinson's disease. *Brain Res* 108:171–191.
- Leenders KL, Villigen S, Brown R (1990) The relationship between "frontal" function in patients with Parkinson's disease and brain dopaminergic activity as measured by PET. *Neurology [Suppl]* 40: 168.
- Lindvall O, Bjorklund A (1984) General organization of cortical monoamine systems. In: *Monoamine innervation of cerebral cortex* (Descaries L, Reader JR, Jasper HH, eds), pp 9–40. New York: Liss.
- Marin J, Rivilla F (1982) Nerve endings and pharmacological receptors in cerebral vessels. *Gen Pharmacol* 13:361–368.
- Mathew RJ, Wilson WH (1985) Dextroamphetamine-induced changes in regional cerebral blood flow. *Psychopharmacology (Berlin)* 87:298–302.
- Mathew RJ, Wilson WH, Tant SR (1986) Determinants of resting regional cerebral blood flow in normal subjects. *Biol Psychiatry* 21: 907–914.
- Matsui T, Hirano A (1978) An atlas of the human brain for computerized tomography. Tokyo: Igakko-Shoin.
- McCulloch J (1984) Role of dopamine and interactions among cerebral functions, metabolism and blood flow. In: *Laboratoires d'Etudes et de Recherches Synthelabo*, Vol 2 (MacKinnon ET, Seylaz J, Bes A, eds), pp 137–155. New York: Raven.
- McCulloch J, Harper AN (1977) Cerebral circulatory and metabolism changes following amphetamine administration. *Brain Res* 121:196–199.
- McNee J, Piercy MF (1952) The relationship of laterality of lesion to performance on Wiegand's sorting test. *J Ment Sci* 98:299–308.
- McHenry L, Merory J, Bass E, Stump DA, Williams R, Witkowski R, Howard G, Toole JF (1978) Xe-133 inhalation method for regional cerebral blood flow measurements: normal values and test-retest results. *Stroke* 9:396–399.
- Milner B (1963) Effects of different brain lesions on card sorting. *Arch Neurol* 9:90–100.
- Moore KE (1978) Amphetamines: biochemical and behavioral actions in animals. In: *Handbook of psychopharmacology*, Vol. 11, Stimulants (Iversen LL, Iversen SD, Snyder SH, eds), pp 41–98. New York: Plenum.
- Nahorski SR, Rogers KF (1973) *In vivo* effects of amphetamine metabolites in metabolic rate in the brain. *J Neurochem* 21:667–686.
- Nakai K, Itakura T, Naka Y, Nakakita K, Kamel I, Imai H, Yokote H, Komai N (1986) The distribution of adrenergic receptors in cerebral blood vessels: an autoradiographic study. *Brain Res* 381:148–152.
- Neuser V, Hoffmeister F (1977) The influence of psychotropic drugs on the local cerebral glucose utilization of the rat brain. In: *CBF VIII—cerebral function, metabolism and circulation* (Ingvar DH, Lason NA, eds), pp 102–103. Copenhagen: Munksgaard.
- Ogura C, Kishimoto A, Takehisa N (1976) Clinical effect of L-dopa in schizophrenia. *Curr Ther Res* 20:308–318.
- Opler LA, Kay SR, Vital-Herne J (1985) Combined mesoridazine and amantadine treatment in refractory schizophrenics. *Curr Ther Res* 37:318–324.
- Overall JE, Gorham DR (1962) The Brief Psychiatric Rating Scale. *Psychol Rep* 10:799–812.
- Petrides M, Milner B (1982) Deficits on subject-ordered tasks after frontal and temporal-lobe lesions in man. *Neuropsychologia* 20:249–262.
- Porrino LJ, Lucignani G, Dow-Edwards D, Sokoloff L (1983) Different anatomical substrates for amphetamine-induced stereotypy and locomotion demonstrated by measurements of local rates of glucose utilization. *J Cereb Blood Flow Metab* 3:S210–S211.
- Raichle ME, Grubb RL Jr, Gado MH, Eichling JO (1976) Correlation between regional cerebral blood flow and oxidative metabolism. *Arch Neurol* 33:523–526.
- Robins TW, Everitt VJ (1987) Psychopharmacologic studies of arousal and attention. In: *Cognitive neurochemistry* (Stahl SM, Iversen SD, Goodman EC, eds), pp 135–170. Oxford: Oxford UP.
- Savasta M, Dubois A, Scutton B (1986) Autographic localization of D₁ dopamine receptors in the rat brain with [³H] SCH 23390. *Brain Res* 375:291–301.
- Sawaguchi (1987) Catecholamine sensitivities of neurons related to a visual reaction time task in the monkey prefrontal cortex. *J Neurophysiol* 58:1100–1122.
- Shenkin HA (1951) Effects of various drugs upon cerebral circulation and metabolism in man. *J Appl Physiol* 3:465–471.
- Shirahata N, Henriksen L, Vorstrup S, Holm S, Lauritzen M, Paulson OB, Lassen NA (1985) Regional cerebral blood flow assessed by Xe-133 inhalation and emission tomography: normal values. *J Comput Assist Tomogr* 9:861–866.
- Siesjo BK (1984) Cerebral circulation and metabolism. *J Neurosurg* 60:883.
- Snyder SH (1977) The dopamine hypothesis of schizophrenia: focus on a dopamine receptor. *Am J Psychiatry* 134:138–143.
- Sokoloff L (1984) Modeling metabolic process in the brain *in vivo*. *Ann Neurol [Suppl]* 15:S1–S11.
- Stokely AIM, Sveinsdottir E, Lassen NA, Rommer P (1980) A single

- photon dynamic computer assisted tomograph (DCAT) for imaging brain function in multiple cross-sections. *J Comput Assist Tomogr* 4:230-240.
- Stuss DT, Benson DF (1983) Frontal lobe lesions and behavior. In: *Localization in neuropsychology* (Kertesz A, ed), pp 429-454. New York: Academic.
- Stuss DT, Benson DF, Kaplan EF (1983) The involvement of orbitofrontal cerebrum in cognitive tasks. *Neuropsychologia* 21:235-248.
- Tamminga CA, Gerlach J (1987) New neuroleptics and experimental antipsychotics in schizophrenia. In: *Psychopharmacology, the third generation of progress* (Miltzer HY, ed), pp 1129-1140. New York: Raven.
- Tassin JP, Simmon H, Herve D, Blanc G, Le Moal M, Glowinski J, Bockaert J (1982) Nondopaminergic fibers may regulate dopamine-sensitive adenylate cyclase in the prefrontal cortex and nucleus accumbens. *Nature* 295:696-698.
- Tassin JP, Studler JM, Herve D, Blanc G, Glowinski J (1986) Contribution of noradrenergic neurons to the regulation of dopaminergic (D-1) receptor denervation supersensitivity in rat prefrontal cortex. *J Neurochem* 46:243-248.
- Vanderwolf CH (1987) Suppression of serotonin-dependent cerebral activation: a possible mechanism of action of some psychotomimetic drugs. *Brain Res* 414:109-118.
- Volkow ND, Wolf AP, Gelder PV, Brodie JO, Overall JE, Cancro R, Gomez-Mont F (1987) Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry* 144:151-158.
- Wechsler LR, Savaki HE, Sokoloff L (1979) Effects of *d*- and *l*-amphetamine on local cerebral glucose utilization in the conscious rat. *J Neurochem* 32:15-22.
- Weinberger DR, Berman KF (1988) Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophr Bull* 14:157-168.
- Weinberger DR, Berman KF, Zec RF (1986a) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Arch Gen Psychiatry* 43:114-124.
- Weinberger DR, Berman KF, Chase TN (1986b) Prefrontal cortex physiological activation in Parkinson's disease: effect of L-dopa. *Neurology [Suppl]* 36:170.
- Weinberger DR, Berman KF, Illowsky B (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. *Arch Gen Psychiatry* 45:609-615.
- Weinberger DR, Gibson R, Coppola R, Jones DW, Sunderland T, Berman KF, Reba RC (1991) The distribution of cerebral muscarinic acetylcholine receptors *in vivo* in patients with dementia: a controlled study with 123-IQNB and SPECT. *Arch Gen Neurol*, in press.
- Weiner N (1972) Pharmacology of central nervous system stimulants. In: *Drug abuse: proceedings of the international conference* (Zarfonetis CJD, ed), pp 243-251. Philadelphia: Lea and Febiger.
- Weiner N (1980) Norepinephrine, epinephrine, and the sympathomimetic amines. In: *The pharmacological basis of therapeutics* (Goodman AG, Gilman A, eds), p 161. New York: Macmillan.
- Wolkin A, Angrist B, Wolf A, Brodie J, Wolkin B, Jaeger J, Cancro R, Rotrosen J (1987) Effects of amphetamine on local cerebral metabolism in normal and schizophrenic subjects as determined by positron emission tomography. *Psychopharmacology (Berlin)* 92:241-246.