Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia

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Both dopaminergic neurotransmission and prefrontal cortex (PFC) function are known to be abnormal in schizophrenia. To test the hypothesis that these phenomena are related, we measured presynaptic dopaminergic function simultaneously with regional cerebral blood flow during the Wisconsin Card Sorting Test (WCST) and a control task in unmedicated schizophrenic subjects and matched controls. We show that the dopaminergic uptake constant K_i in the striatum was significantly higher for patients than for controls. Patients had significantly less WCST-related activation in PFC. The two parameters were strongly linked in patients, but not controls. The tight within-patient coupling of these values, with decreased PFC activation predicting exaggerated striatal 6-fluorodopa uptake, supports the hypothesis that prefrontal cortex dysfunction may lead to dopaminergic transmission abnormalities.

The importance of dopaminergic mechanisms in the pathophysiology of schizophrenia was inferred from the link between the antipsychotic efficacy of neuroleptic drugs and their affinity for the dopaminergic D_2 receptor[1]. Frontal cortex dysfunction in this disorder has been posited even longer, since the modern conceptualization of schizophrenia[2]. Neuroimaging and basic research provide ample evidence for abnormalities in both these domains in schizophrenia[3,4].

A crucial question has been whether and how these pathophysiological phenomena interact. Because interference with prefrontal cortex dopamine inputs or intrinsic prefrontal efferents can lead to disinhibited striatal dopamine function in the rat[5,6], it has been proposed that exaggerated striatal dopaminergic neurotransmission in schizophrenia might result from dorsolateral prefrontal cortical dysfunction[7,8]. This proposal, which has been extended by several investigators[9,10], leads to the specific hypothesis that, in patients, elevated striatal dopaminergic function should be predicted by the degree to which PFC function is disturbed, whereas no such relationship should exist in control subjects without PFC pathophysiology.

The present study was designed to test this hypothesis. We used positron emission tomography (PET) to measure both regional cerebral blood flow (rCBF, with $[^{15}O]H_2O$) and presynaptic dopaminergic function using the tracer 6-[^{18}F]DOPA (6-FD) in the same session. Schizophrenic subjects withdrawn from medication for four weeks and matched normal controls were studied during the Wisconsin Card Sorting Test, an abstract reasoning, working memory task commonly used to investigate PFC abnormalities[11]. Because the vast majority of studies indicate that hypoactivation is the signature of PFC dysfunction in PET during this task[12], we predicted that decreased activation during the WCST should be inversely correlated with striatal 6-FD uptake in the patient group. Using the outlined multitracer imaging approach, we found decreased PFC blood flow in patients during the WCST, and an increase in striatal 6-FD uptake in schizophrenics relative to healthy subjects. Confirming our main hypothesis, patients showed highly significant inverse correlation of these two measures, but controls did not.

Results

Behavior

Patients and control subjects completed the same number of trials during the WCST (119.3 versus 116.2, respectively; $Z = 1.28$, $p > 0.2$). However, patients made significantly more perseverative errors (8.6 versus 27.8; $Z = -2.56$, $p < 0.02$) and attained fewer categories (9.1 versus 4.1; $Z = 2.56$, $p < 0.02$) than control subjects.

Regional cerebral blood flow and dopamine uptake

Analysis of rCBF subtraction maps showed that the WCST significantly activated a region in the right dorsolateral prefrontal cortex (x, y, z; 40, 8, 44 mm; $p < 0.001$, $T = 6.98$, $Z = 4.12$) in both groups (**Fig. 1a**). Additional foci of activation were observed in the right inferior parietal lobule (32, –58, 24 mm; $p < 0.001$, $T = 4.08$, $Z = 3.06$), occipital cortex (–30, –86, –8 mm; $p < 0.001$,

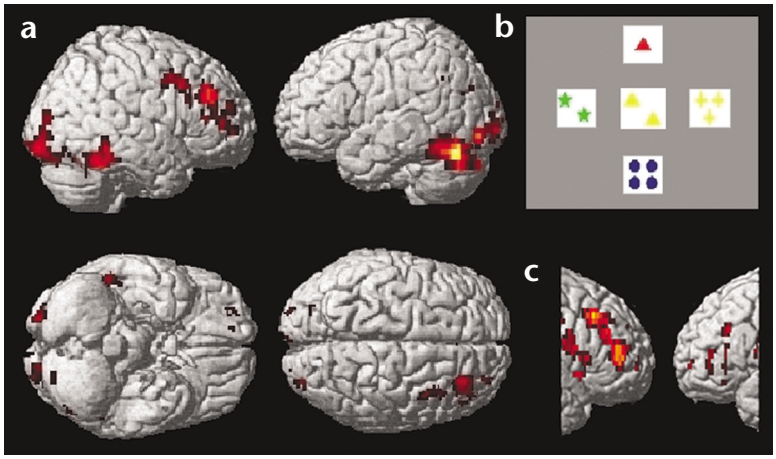

Fig. 1. Statistical maps of regional cerebral blood flow. (**a**) Conjunction analysis showing voxels with significantly ($p < 0.01$, voxel level) higher rCBF during the task than the control task. (**b**) Computer screen showing the Wisconsin Card Sorting Test stimuli. (**c**) Voxels showing significantly ($p < 0.05$) higher rCBF in the task-minus-control contrast in the frontal lobes of controls as compared to patients.

$T = 7.87$, $Z = 4.35$) and cerebellum (–22, –94, –12 mm; $p < 0.001$, $T = 6.70$, $Z = 4.04$) and, to a lesser degree, left inferior parietal lobule (–36, –58, 36 mm; $p < 0.005$, $T = 3.29$, $Z = 2.56$).

This system was less activated in patients, with the right DLPFC showing the maximal prefrontal between-group difference in rCBF activation (**Fig. 1c**; 34, 36, 40 mm, BA 9; $p < 0.005$, voxel-level uncorrected; $p < 0.001$, cluster-level corrected). When rCBF data during the WCST were analyzed separately, values in the region of interest were also significantly lower in patients than in control subjects (relative cerebral blood flow, 60.3 versus 55.2; brain average, 50; $Z = 2.08$, $p < 0.04$).

In the striatal region of interest, dopamine uptake, measured by F-DOPA K_i, was significantly higher for patients (0.0100 per min) than for normal controls (0.0084 per min; **Fig. 2a**; $Z = –2.40$, $p < 0.02$).

Correlation between PFC rCBF and striatal K_i

Patients showed a highly significant negative correlation between task-related activation (task minus control) in the right DLPFC ROI and striatal K_i (Spearman's $r = –0.943$, $p < 0.005$; **Fig. 2b**), which was absent in controls (Spearman's $r = –0.086$, $p > 0.85$). A similar result was found for striatal K_i and rCBF during the WCST task itself, which also was negatively correlated only in patients (Spearman's $r = –0.829$, $p < 0.05$; **Fig. 2c**). No correlation was found in the control group (Spearman's $r = 0.371$, $p > 0.45$; **Fig. 2d**). This between-groups difference in correlation of rCBF with striatal K_i itself was significant (William-Pearson test, $p = 0.027$ for task-related blood flow, $p = 0.0376$ for WCST minus control activation). There was no significant correlation with blood flow during the control task ($p = 0.17$).

Post-hoc analyses

After testing the main hypothesis, we did several post-hoc analyses for further clarification. Voxel-by-voxel K_i maps were compared between groups using statistical parametric mapping. This confirmed the results from the ROI analysis in showing striatal voxels with significantly increased K_i in the patient group and further demonstrated that the increase was most marked on the left side (maximum –28, –10, –4 mm; $p < 0.001$, voxel-level uncorrected; $p < 0.001$, cluster-level corrected). No significant laterality effects in striatal K_i were found, and similar correlations were observed in both hemispheres. There were no cortical areas in which 6-FD function differed significantly between the groups in this analysis. Average K_i in the dorsolateral prefrontal ROI was also examined separately; again, no significant difference was found between patients (average K_i, 0.00008 per min) and controls (0.00010 per min, $p = 0.34$).

Striatal K_i showed significant correlations with behavioral performance in patients, but not controls. In the patient group, the higher the K_i, the higher the percentage of perseverative errors (Spearman's $r = 0.829$, $p < 0.05$) and the fewer categories attained (Spearman's $r = –0.829$, $p < 0.05$). To investigate whether this could be ascribed to a secondary correlation effect, we performed a stepwise multiple regression entering the performance parameters and prefrontal blood flow activation as the explanatory variables. The independent variable was K_i. Indeed, we found that the task-related prefrontal blood flow was significant, but none of the performance parameters was significant (β for task-related rCBF, –0.81, $p < 0.01$; highest β for behavioral measures, categories attained, $\beta = –0.22$, $p > 0.3$). No correlation was found with the number of trials in patients, or with any parameter in the control group.

Finally, to test whether the observed correlation of prefrontal cortex activation with dopamine uptake was specific for this brain region, we calculated average blood flow in an ROI comprising voxels in another region significantly activated by the task in the occipitotemporal cortex (outside the reference region used for the input function). Here, no correlation with striatal K_i was found in either group. We also analyzed an ROI in the inferior parietal lobule on the right, an area that does project heavily upon the striatum and is involved in working memory performance. Again, no significant correlation with striatal K_i was found in either group.

Discussion

In this study, striatal F-DOPA uptake was found to be significantly increased in schizophrenic patients, in agreement with four previous reports[13–16] as opposed to one equivocal[17] and one negative study[18]. Because the accumulation of this tracer is due to dopa decarboxylase, an enzyme whose activity, although not rate limiting, reflects a regulated aspect of presynaptic dopamine synthesis[19,20], these results show that presynaptic dopaminergic function is exaggerated in the striatum of schizophrenic subjects. This agrees with compelling data indicating increased amphetamine-induced striatal dopamine release[21]. Increased dopaminergic neurotransmission in the striatum of schizophrenics can also be inferred from elevated baseline D_2 receptor occupancy, a phenomenon proposed in the mid-eighties[22] that has recently been demonstrated[23].

The key purpose of the present study was to test for the existence of an inverse correlation between PFC activation and striatal dopaminergic function in schizophrenia. In accordance with this *a priori* hypothesis[8], we indeed demonstrated that the measured indicator of neuronal activation, the increase in blood flow during the WCST task, was tightly coupled with striatal K_i in patients, but not in controls. As predicted, the less

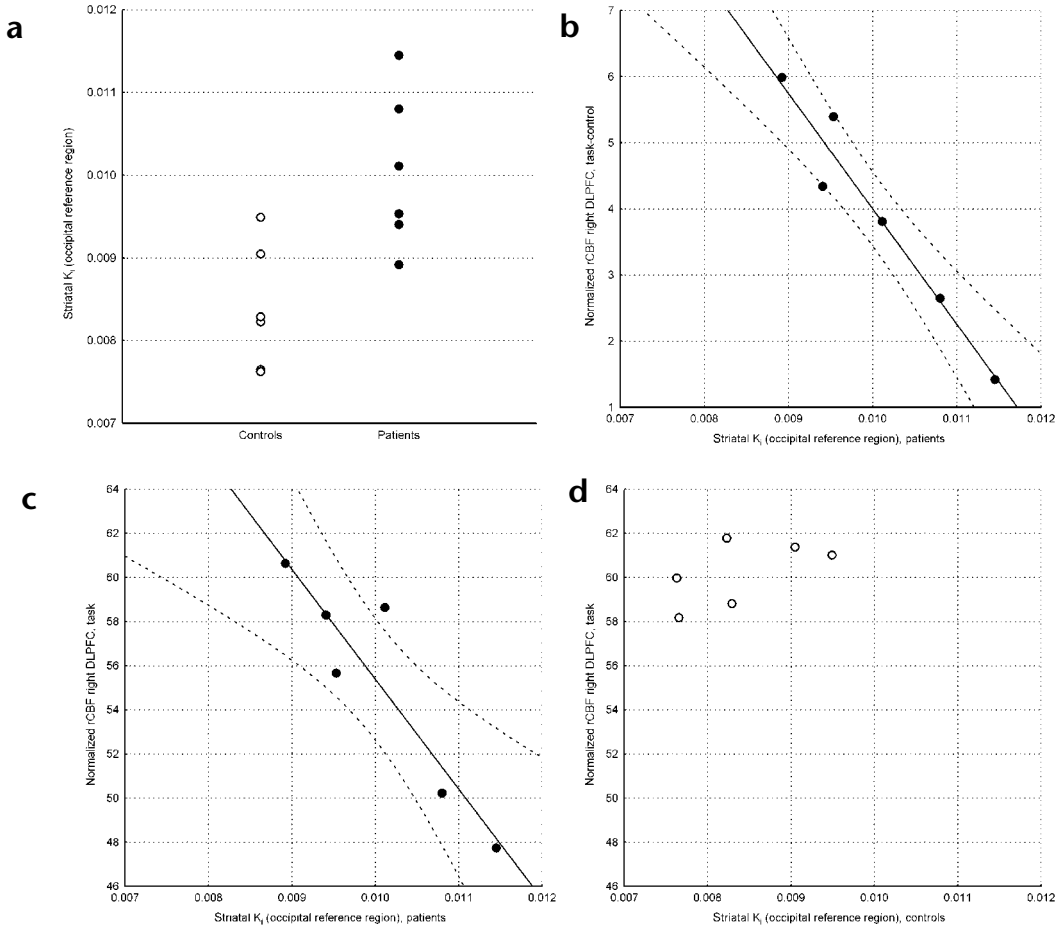

Fig. 2. Striatal dopamine uptake (K_i) and relationship with DLPFC blood flow. (**a**) Significantly ($Z = -2.40$, $p < 0.02$) increased K_i in schizophrenic patients. (**b**) Significant correlation of K_i with blood flow change, task minus control, in patients (right-sided DLPFC ROI, bilateral striatal ROI, Spearman's $r = -0.943$, $p < 0.005$, regression line with 95% confidence bands). (**c**) Significant correlation of K_i with blood flow during the Wisconsin Card Sorting task in patients (Spearman's $r = -0.829$, $p < 0.05$). (**d**) No significant correlation in controls (Spearman's $r = 0.371$, $p > 0.45$).

activation found in the DLPFC, the more abnormal the increase in K_i, demonstrating strong coupling of cortical and dopaminergic dysfunction in the disorder. Our comparison with an occipital region of interest, where no such correlation existed, argues for the specificity of this finding for the dorsolateral prefrontal region. The finding that a correlation existed only in the patient population but not in the control group suggests that the observed interaction was related to the pathology present in patients, as hypothesized.

As stated, we believe that the observed tight correlation provides evidence for primary dysfunction of the prefrontal cortex in schizophrenia leading to pathologically increased presynaptic dopaminergic function. This concept is also consistent with earlier data demonstrating a correlation, again only in patients, between decreased N-acetyl-aspartate, a magnetic resonance spectroscopy marker of neuronal integrity in the DLPFC and exaggerated amphetamine-induced dopamine release[24]. The current data suggest that the presence of increased presynaptic DA stores could interact with the pharmacological action of amphetamine in releasing presynaptic DA[7].

Basic research strongly supports the concept that the activity of dopamine terminals in the striatum is under control of the PFC. Although differing in details about the mechanism or directionality, a number of animal studies show that stimulation or inhibition of PFC function affects firing rates of subcortical neurons as well as dopamine release[25,26]. The mechanism of regulation is complex, involving direct and indirect projections from the cortex to brainstem and striatum. This feedback is primarily exerted through glutamatergic efferents from the PFC[27]. In humans, disruption of glutamatergic neurotransmission with ketamine leads to increased amphetamine-induced dopamine release in the striatum[28]. Importantly, in the rodent[29], PFC afferents to midbrain neurons projecting to the striatum are selectively located on GABAergic (inhibitory) neurons, suggesting a direct anatomical mechanism by which a pathological decrease in PFC excitatory output would lead to disinhibition of striatal dopaminergic function. This anatomical account is also consistent with the proposal[30] that prefrontal cortical glutamatergic projects are a 'brake' on the striatal dopamine system.

Our data may also have implications for understanding the nature of the neuropathology underlying these pathophysiological relationships. Although it is unclear whether all disturbances in PFC function would be associated with increased striatal dopamine metabolism, studies in animals have demonstrated that developmental disruption of temporolimbic connections to

the PFC do produce such effects. Indeed, exaggerated striatal dopamine release was found in monkeys with a neonatal temporolimbic lesion[31]. Analogous developmental abnormalities in PFC connectivity have been implicated in schizophrenia[7].

Because correlative measures cannot establish causality, other explanations for the observed within-patient correlation between striatal 6-FD uptake and cortical function also need to be considered. The data might reflect a primary disturbance at the level of the basal ganglia, in which excessive dopaminergic function, via disturbed gating[32], could lead to functionally deficient prefrontal activation. However, direct support for such a mechanism on the prefrontal–striatal level is lacking. Moreover, this interpretation would not explain the finding in schizophrenia that decreased NAA in DLPFC predicts the striatal dopamine release after amphetamine[24], which argues for intrinsic cellular pathology. It is tempting to speculate whether the prefrontal cortical activation deficit observed is secondary to alterations of dopamine function at the level of the cortex, via the mesocortical tract, which mirrors the alteration seen at the striatum. However, available evidence suggests cortical dopaminergic tone is decreased in schizophrenia[33]. This evidence includes improved PFC function in the disease after administration of dopamine agonists[34], positive correlation between cerebrospinal fluid homovanillic acid and PFC rCBF during the WCST in patients[8], and D_1- receptor density shown by imaging studies in the cortex of patients[35]. In agreement with these studies, our data do not show increased presynaptic dopamine turnover in the cortex, a finding that must however be seen in the context of low signal-to-noise ratio in the cortex due to the lower density of dopaminergic innervation as compared to the striatum.

Aside from the small sample size, a potential confound in our study is that our patients were previously medicated and withdrawn from medication before scanning, which even after a month might have residual effects on striatal dopamine metabolism. However, both prefrontal dysfunction and increased striatal K_i have been observed in drug-naive as well as previously medicated patients, making this potential confound a less likely basis of our findings. F-Dopa uptake may also be altered in smokers, a condition present in two of the patients studied; however, their striatal K_i and prefrontal blood flow did not differ significantly from those of the other patients ($p > 0.16$–0.35).

Abnormal K_i predicted impaired task performance as well as DLPFC hypoactivation. Because of the strong linkage between K_i and PFC dysfunction in our patient group, this is explained as a secondary correlation, consistent with the multiple regression analysis. Moreover, direct manipulation of striatal dopamine in the rat does not influence working memory performance[36], and most primate data on the dopaminergic regulation of working memory-related activation of the prefrontal cortex implicate prefrontal dopamine[37,38].

In summary, using a multi-tracer imaging approach, we demonstrated a tight within-patient coupling of decreased PFC activation and exaggerated striatal 6-FD uptake in patients with schizophrenia. This provides direct evidence for a common pathophysiological mechanism linking these abnormalities[39] and can be a model for other neuropsychiatric disorders in which a primary disturbance based in cortical function or structure leads to neurochemical counteradaptation.

Methods

Six patients (age 25–43 years, mean 35 years, 1 female) with DSM-IIIR-diagnosed schizophrenia[40] participated in this study. They had been treated with typical neuroleptics (haloperidol) in the past and were withdrawn from all medication four weeks before the experiment. Six healthy subjects (without neuropsychiatric signs or history and not on medication), each individually chosen (before scanning) to be of the same sex and handedness and within three years of age of a patient, were studied as a control group (age 24–41 years, mean 34 years, 1 female). All subjects participated after giving informed consent as approved by the National Institute of Mental Health Institutional Review Board and the Radiation Safety Committee. Subjects abstained from caffeine and nicotine for 4 hours before the scanning session, and they were pretreated with 100 mg of Carbidopa to reduce peripheral metabolism of 6-FD and, thus, increase availability of this tracer in the brain[41].

Participants first underwent a computerized version of the WCST and a matched sensorimotor control task[42] while regional cerebral blood flow was measured after a bolus of 40 mCi [^{15}O]-H_2O. Fifteen contiguous tomographic slices (one volume) for each condition were acquired on a Scanditronix PC2048-153 camera (FWHM 6.5 mm). The rCBF data were aligned[43], normalized to a template image and smoothed with a 12 mm isotropic Gaussian filter. We calculated rCBF relative to a whole brain mean of 50. Subtraction images of rCBF during the WCST compared to the control task were created and analyzed using SPM99. Coordinates of statistically significant brain activations are reported according to the system described in the Talairach-Tournoux atlas[44].

Approximately 12 minutes after the rCBF scans, 4.5 mCi of 6-FD was infused over 45 seconds, and images were acquired from the time of infusion up to 120 minutes later (27 images total), while subjects performed the WCST task. The 6-[^{18}F]DOPA data were aligned in-plane and registered[43], coregistered to the rCBF scans, and affine normalized. Irregular regions of interest were drawn around the basal ganglia (roughly corresponding to a threshold of 3 times the mean activity), resulting in a bilateral region of interest. Using the time–activity curve in an occipital reference region as the input function[45], the kinetic rate constant K_i for striatal dopaminergic uptake was calculated voxel-by-voxel using a linear fit based on the Patlak method[46].

To test the hypothesis that prefrontal function was coupled to 6-FD uptake, we used a conjunction analysis to define a region of interest (ROI) comprising all voxels in the prefrontal cortex significantly ($p < 0.01$, voxel level) activated by the task in both groups, derived by manually selecting all voxels in prefrontal cortex significant at the chosen threshold. This resulted in a right-sided DLPFC region (**Fig. 1a**). The average rCBF in this region was then correlated with the K_i. Group differences were tested nonparametrically using the Mann-Whitney U test. Spearman's r was used for correlations, and the Williams-Pearson test was used to assess whether correlations differed significantly between the patient and the control groups.

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