Regular Articles

Specific Relationship Between Prefrontal Neuronal *N*-Acetylaspartate and Activation of the Working Memory Cortical Network in Schizophrenia

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Objective: Abnormal activation of the dorsolateral prefrontal cortex and a related cortical network during working memory tasks has been demonstrated in patients with schizophrenia, but the responsible mechanism has not been identified. The present study was performed to determine whether neuronal pathology of the dorsolateral prefrontal cortex is linked to the activation of the working memory cortical network in patients with schizophrenia. **Method:** The brains of 13 patients with schizophrenia and 13 comparison subjects were studied with proton magnetic resonance spectroscopic (^{1}H-MRS) imaging (to measure *N*-acetylaspartate as a marker of neuronal pathology) and with [^{15}O]water positron emission tomography (PET) during performance of the Wisconsin Card Sorting Test (to measure activation of the working memory cortical network). An independent cohort of patients (N=7) was also studied in a post hoc experiment with ^{1}H-MRS imaging and with the same PET technique during performance of another working memory task (the "N-back" task). **Results:** Measures of *N*-acetylaspartate in the dorsolateral prefrontal cortex strongly correlated with activation of the distributed working memory network, including the dorsolateral prefrontal, temporal, and inferior parietal cortices, during both working memory tasks in the two independent groups of patients with schizophrenia. In contrast, *N*-acetylaspartate in other cortical regions and in comparison subjects did not show these relationships. **Conclusions:** These findings directly implicate a population of dorsolateral prefrontal cortex neurons as selectively accounting for the activity of the distributed working memory cortical network in schizophrenia and complement other evidence that dorsolateral prefrontal cortex connectivity is fundamental to the pathophysiology of the disorder.

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Working memory is a cognitive construct describing the ability to hold information transiently in mind in the service of comprehension, thinking, and planning (1, 2). Complex cognitive processes such as working memory are thought to be subserved by the functional integration of interconnected regions forming large-scale cortical networks (1–5). Data on human and nonhuman primates show that a key cortical region for the execution of working memory tasks is the dorsolateral prefrontal cortex (6–12), which has reciprocal anatomical connections with the parietal, tempo-

ral, and cingulate cortices, which also participate in the cortical network related to working memory (1–5).

Deficits in working memory have been reported to be a cardinal feature of the pathophysiology of schizophrenia (13, 14). Attempts to anatomically localize these deficits with functional neuroimaging studies in patients performing working memory tasks have often shown subnormal activation of the dorsolateral prefrontal cortex and, to a lesser extent, abnormalities of other regions in the working memory network (15–22). There has been considerable debate on issues involving the mechanism of this pattern of hypofunction, including whether it reflects distributed neuronal pathology, is referable to focal cortical pathology, or is, perhaps, an artifact of the test procedure (15–22). Postmortem studies of the brains of patients with schizophrenia have shown evidence of abnormalities in a number of cortical areas within the working memory network, including the dorsolateral prefrontal cortex, cingulate, and temporal cortices (23–26), although the most extensive data have implicated the dorsolateral prefrontal cortex (27–32). Since the overall function of a cortical network presumably relies on the competence of both local information processing within specific local circuits and axonal connections between local circuits and distant cortical areas, a deficit of a single region, for example the dorsolateral prefrontal cortex, could conceivably have functional reverberations throughout the working memory network. The purpose of the present study was to address directly the question of whether the integrity of a population of neurons within the dorsolateral prefrontal cortex, as studied with proton magnetic resonance spectroscopic (^{1}H-MRS) imaging, preferentially accounts for the distributed pattern of cortical function associated with working memory in schizophrenia, as studied with [^{15}O]water positron emission tomography (PET) during performance of working memory tasks.

^{1}H-MRS imaging detects signals in multiple brain regions arising from *N*-acetyl-containing moieties (mainly *N*-acetylaspartate, NAA), choline-containing compounds (CHO), and creatine plus phosphocreatine (CRE) (33). NAA is an intraneuronal amino acid, the highest concentrations of which occur in pyramidal neurons (34). Its biological role has yet to be clearly defined. However, it acts through the glutamatergic *N*-methyl-D-aspartic acid (NMDA) receptor to elevate intracellular calcium (35), and its concentrations are reduced by pharmacological inhibition of mitochondrial energy metabolism (36) and by a number of pathological processes affecting the integrity of neurons (37, 38). It is interesting that a recent study (39) has also shown increased NAA measures in rats during experimental status epilepticus, suggesting that NAA correlates with the functional status of neurons. Relative concentrations of NAA have been previously shown to be lower than normal in the prefrontal cortex of patients with schizophrenia (40–44).

[^{15}O]Water PET identifies changes in regional cerebral blood flow (rCBF) associated with neuronal activity. In the first of two experiments we measured rCBF during performance of the Wisconsin Card Sorting Test, an abstract reasoning task involving the use of previously learned information to formulate a strategy for present and future actions. To the extent that recent memory is essential for achieving the correct action, the test has been considered to involve working memory and to be sensitive to prefrontal pathology (10, 15, 16, 45, 46). Several earlier studies (15–19) have shown reduced rCBF in the dorsolateral prefrontal cortex and other related cortical areas in patients with schizophrenia during performance of the Wisconsin Card Sorting Test and other tasks involving working memory. We also performed a second, post hoc experiment to address the issue of whether the correlations found in the patients during the Wisconsin Card Sorting Test are task specific or related to generic working memory function. In this second experiment, a separate group of patients with schizophrenia performed a less complex working memory task, a version of the "N-back" task (47). This task has been previously shown to produce activation in a cortical network including the same regions involved in the Wisconsin Card Sorting Test and to reveal similar pathophysiological characteristics in patients with schizophrenia (22, 48). A "2-back" condition, in which subjects respond according to a number seen two stimuli before, requires continuous updating of the mental set and the use of working memory (22).

METHOD

Subjects

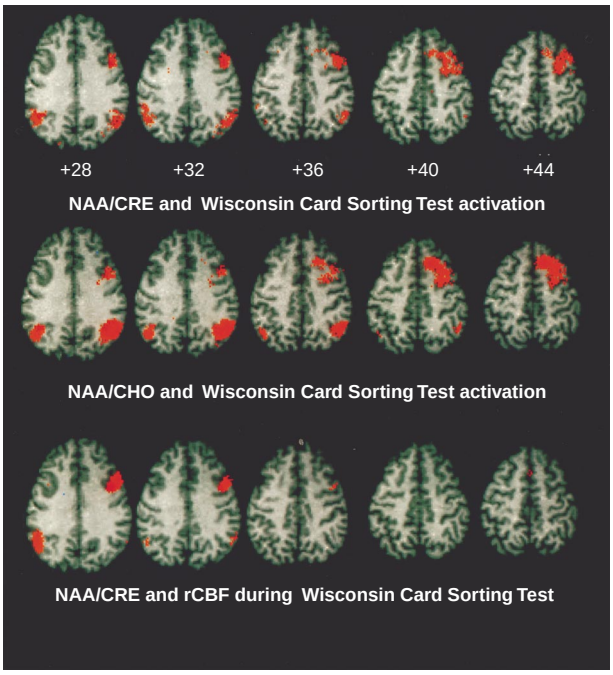
For the Wisconsin Card Sort study, there were 26 subjects: 13 patients with a diagnosis of schizophrenia according to DSM-IV criteria (11 men; mean age=35.0 years, SD=8.6) and 13 comparison subjects (eight men; mean age=34.6 years, SD=8.0). Each subject underwent ^{1}H-MRS imaging and [^{15}O]water PET on two different days. For the ^{1}H-MRS imaging scan, five of the patients had been without drugs for at least 3 weeks, while the others were receiving neuroleptics. Neuroleptics have been previously shown not to affect NAA findings (43, 49). On the day of the PET scan, five of the patients who had been receiving drugs when studied with ^{1}H-MRS imaging were being treated with clozapine, while the others had been drug free for at least 3 weeks. The patients and comparison subjects had similar performances on the Wisconsin Card Sorting Test, as expressed by the average percentage of correct responses (patients, 71%; comparison subjects, 74%). The N-back study involved a different group of seven patients (five men; mean age=31.8 years, SD=8.7) with a diagnosis of schizophrenia according to DSM-IV. They had all been without neuroleptics for at least 2 weeks (range=15–30 days) before both the ^{1}H-MRS imaging and [^{15}O]water PET scans. The average performance of the patients on the 2-back version of the task was 50%, which is well below that reported for normal subjects (82%) (22).

After complete description of all studies to the subjects, written informed consent was obtained from each and every subject.

^{1}H-MRS Imaging Procedure

The ^{1}H-MRS imaging studies were performed as previously described (33, 41, 43) on a conventional GE Signa 1.5-T nuclear magnetic resonance imaging system. The ^{1}H-MRS imaging pulse sequence acquires four spectroscopic slices (TR=2200 msec, TE=272 msec) involving 32 × 32 phase-encoding steps over a 240-mm field

FIGURE 1. Voxel-by-Voxel Correlations Between Metabolite Ratios for the Dorsolateral Prefrontal Cortex of 13 Schizophrenic Patients and Blood Flow Activation During the Wisconsin Card Sorting Test[a]



[a] The slices are identified by position on the z axis (Talairach coordinate). The first row shows, in red, voxels with significant positive Pearson correlations (r>0.68, p<0.01) between the ratio of *N*-acetylaspartate to creatine plus phosphocreatine (NAA/CRE) and activation of regional cerebral blood flow (rCBF) during the Wisconsin Card Sorting Test (test condition minus control condition). The second row shows areas of significant correlations between the ratio of *N*-acetylaspartate to choline-containing compounds (NAA/CHO) and rCBF activation during the Wisconsin Card Sorting Test. The third row shows significant correlations between NAA/CRE and rCBF during the Wisconsin Card Sorting Test alone.

of view for each slice. Each volume element (voxel) has nominal dimensions of 7.5 mm × 7.5 mm × 15 mm (0.84 ml). Actual volume, based on full width at half maximum after filtering of k-space, is 1.4 ml. The ^{1}H-MRS imaging data processing involved locating NAA, CHO, and CRE in spectra from each voxel and then displaying the four 32 × 32 arrays showing spatial variation of the magnitude of each of the signals in each of the slices. Regions of interest were drawn on coplanar magnetic resonance imaging scans as previously described (41). The metabolites were studied as ratios of the area under each peak: NAA/CRE, NAA/CHO, CHO/CRE.

[^{15}O]Water PET Procedure

For the Wisconsin Card Sorting Test study, each subject underwent two PET scans during a single session: one scan while performing the card sorting test and the other one while performing a sensorimotor control task. The PET data were acquired as described by Berman et al. (10) on a Scanditronix PC2048-15B PET scanner that simultaneously produces 15 contiguous slices in 16 frames over 4 minutes. An intravenous bolus of approximately 42 mCi of [^{15}O]water was administered before each scan. Arterial input functions were measured with automated arterial blood sampling, and absolute rCBF (milliliters of blood per minute per 100 g of tissue) was calculated for each voxel. For the N-back task study, 60-second PET data were acquired nonquantitatively on a GE Advance PET camera in three-dimensional mode after a bolus injection of 10 mCi of [^{15}O]water per scan. Images for each subject were registered by using the Automated

TABLE 1. Brain Locations of Maximal Positive Correlations Between Blood Flow Activation[a] During the Wisconsin Card Sorting Test and the Ratio of *N*-Acetylaspartate to Creatine Plus Phosphocreatine in the Dorsolateral Prefrontal Cortex of 13 Schizophrenic Patients

Anatomical Location	Brodmann's Areas	Talairach Coordinates x	y	z	r
Left					
Gyrus frontalis inferior/ gyrus precentralis	44/6	–30	–8	32	0.83
Gyrus frontalis medius	9	40	16	36	0.81
Gyrus frontalis inferior	46	40	42	8	0.78
Gyrus supramarginalis					
Site 1	39/40	28	–52	36	0.77
Site 2	39/40	–32	–56	32	0.76
Gyrus occipitalis medius	18	–26	–88	20	0.81
Right					
Gyrus frontalis inferior					
Site 1	44	46	4	32	0.87
Site 2	45/46	40	40	4	0.74
Gyrus frontalis medius	9	–30	18	36	0.70
Gyrus supramarginalis/ gyrus temporalis superior	39/40	52	–58	32	0.84
Gyrus temporalis superior	39	–46	–58	28	0.81

[a] Regional cerebral blood flow (rCBF) during the test minus rCBF during a control task.

Image Registration (AIR) program and then normalized to the atlas of Talairach and Tournoux (50) and smoothed with a 15 × 15 × 5 filter by using the SPM95 package. The PET data were normalized by expressing each value as a ratio to the global mean. To determine activation during the Wisconsin Card Sorting Test, we subtracted the rCBF during the control condition from that during the Wisconsin Card Sorting Test. For the N-back study, activation data were derived by subtracting the average rCBF for seven scans acquired during the 2-back condition from the average for two scans acquired during rest. Pearson correlations between the ^{1}H-MRS imaging regional values and rCBF PET data during the Wisconsin Card Sorting Test were determined on a voxel-by-voxel basis. The statistical threshold used was p<0.01, corresponding to a Pearson r of 0.683. A cluster threshold of 10 contiguous voxels was applied as well. Because of the smaller group in the N-back study, we used a Spearman correlation analysis to avoid a potential outlier effect.

RESULTS

^{1}H-MRS Imaging Measures and Brain Activation During Wisconsin Card Sorting Test

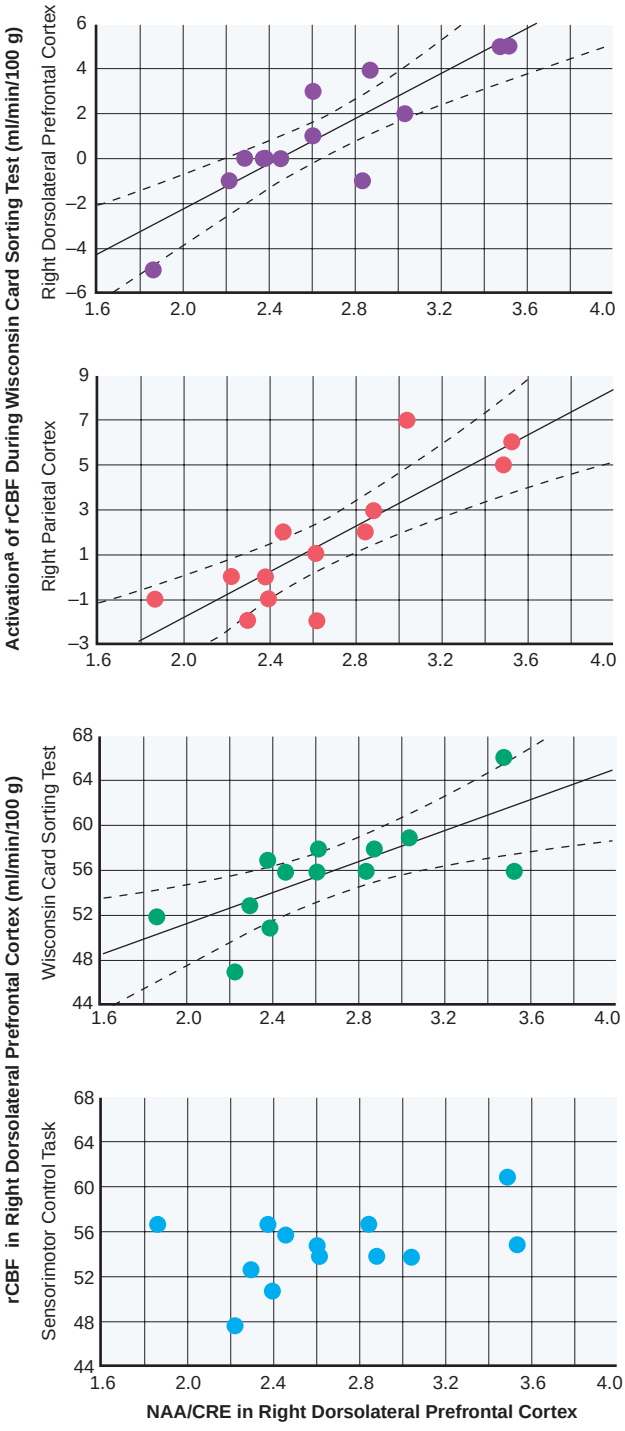
In the patients, NAA/CRE in the dorsolateral prefrontal cortex was strongly and positively correlated with activation in the prefrontal cortex (Brodmann's areas 9, 10, 44, 45, 46), parietal cortex (Brodmann's area 39/40), and temporal association cortex (figure 1 and table 1). NAA/CRE in the dorsolateral prefrontal cortex also exhibited negative correlations, mostly with subcortical structures, including the cerebellum and basal ganglia. On the other hand, NAA/CRE in the dorsolateral prefrontal cortex of the comparison subjects showed a different pattern of relationships with rCBF activation, correlating only in a few scattered voxels in the left inferolateral prefrontal cortex and not with any other region activated by the Wisconsin Card Sorting Test.

Because it is impossible to perform absolute measurements of metabolites with our ^{1}H-MRS imaging technique and because we wished to test whether the relationships in patients with schizophrenia were specifically attributable to NAA signals, we also examined the correlations of two other ratio measures, NAA/CHO and CHO/CRE, in the dorsolateral prefrontal cortex to rCBF activation. While NAA/CHO correlated with activation in exactly the same Brodmann's areas as seen with NAA/CRE (figure 1), CHO/CRE showed only sporadic correlations and none in the areas associated with working memory. Even though absolute concentrations of the metabolites were not studied, this consistent pattern of correlations indicates that they arise from abnormalities in NAA. These results suggest that the integrity of a population of neurons in the dorsolateral prefrontal cortex and their connections predict the activation of the whole working memory cortical network in patients with schizophrenia.

We also tested whether the correlations between NAA measures and activation were specific to NAA measures in the dorsolateral prefrontal cortex. We examined correlations between NAA/CRE in the hippocampal area (also shown to have low NAA measures in schizophrenia [40, 42, 46, 47, 51, 52]), superior temporal gyrus, anterior cingulate, and occipital cortex (regions that are activated during working memory tasks) and the rCBF activation data. Few sporadic correlations emerged, and none of these involved areas of rCBF activation in the working memory network. Therefore, these additional data suggest that the correlation between NAA relative measures in the dorsolateral prefrontal cortex and activation in the cortical working memory network is regionally specific.

We also examined whether the correlations between NAA measures in the dorsolateral prefrontal cortex and rCBF activation (obtained by subtraction of blood flow during the control task from blood flow during the Wisconsin Card Sorting Test) were related to blood flow changes during working memory per se, rather than to blood flow during any volitional task. We performed separate correlations between NAA/CRE in the dorsolateral prefrontal cortex and rCBF during the two components of the rCBF activation signal, the Wisconsin Card Sorting Test and the control task. While the results of the correlations with rCBF during the Wisconsin Card Sorting Test showed the same pattern of correlations as with the activation data (figure 2), there were few correlations during the control task and these involved brain areas not activated by the working memory task. Therefore, the correlations between NAA measures and activation are likely due to rCBF changes during working memory.

FIGURE 2. Correlations Between the Ratio of *N*-Acetylaspartate to Creatine Plus Phosphocreatine (NAA/CRE) and Regional Cerebral Blood Flow (rCBF) in Areas of the Dorsolateral Prefrontal Cortex of 13 Patients With Schizophrenia During the Wisconsin Card Sorting Test and a Control Task



[a] rCBF during the test minus rCBF during the control task.

^{1}H-MRS Imaging Measures and Brain Activation During N-Back Task

In this post hoc experiment, we addressed several issues, including the reproducibility of the data in another cohort of patients, whether the correlations are task specific or related to generic working memory function, and the possible impact of antipsychotic medication. NAA/CRE in the dorsolateral prefrontal cortex of these patients was also positively correlated

with activation in the same brain regions (as identified by the local maxima of the activation) found during the Wisconsin Card Sorting Test study, including the prefrontal cortex (r_s=0.86, N=7, p<0.01) and the temporal-parietal cortex (r_s=0.84, N=7, p<0.01). These data suggest that the correlations are reproducible in another group of patients with schizophrenia and that they are typical of tasks engaging the working memory circuitry, regardless of the specific test used. These additional results also indicate that the correlations are not due to active treatment with antipsychotic drugs, as this entire cohort was drug free, and not dependent on task performance per se, as the same relationships were found during this working memory task, on which the patients' performance was abnormal, and during the Wisconsin Card Sorting Test, on which a different cohort of patients and comparison subjects did not differ.

DISCUSSION

Our results show that in schizophrenia the functional integrity of neurons within the dorsolateral prefrontal cortex (as represented by NAA measures) has predictable physiological reverberations throughout the entire working memory cortical network. NAA measures in the dorsolateral prefrontal cortex predict activation of cortical regions involved in the execution of working memory tasks, including the dorsolateral prefrontal cortex itself, the parietal cortex, and the temporal association cortex. Moreover, these relationships are regionally specific, involving only the dorsolateral prefrontal cortex as a predictor of network activation. The lack of such relationships in healthy subjects suggests that they emerge in patients because of disease-associated neuronal pathology in the dorsolateral prefrontal cortex. In the present subjects, as in our previous study groups (41, 43), NAA measures in the dorsolateral prefrontal cortex of patients (averaged bilateral NAA/CRE: mean=2.6, SD=0.4) were significantly lower than those of normal comparison subjects (mean=2.9, SD=0.3) (two way ANOVA: F=4.5, df=1, 24, p<0.04; no effect of side or side-by-group interaction). To the extent that low NAA measures are a reflection of impaired functional integrity of neurons, this putative impairment constrains in a predictable way the functional capacity of the distributed working memory network, as if these dorsolateral prefrontal cortex neurons by virtue of their projections constitute a rate-limiting factor for the degree of network recruitment (48). These results are consistent with the anatomical and physiological centrality of the dorsolateral prefrontal cortex with respect to working memory function (6–12) and, perhaps, with respect to the pathophysiology of schizophrenia.

A traditional criticism of functional neuroimaging studies assessing differences in activation by working memory tasks between patients with schizophrenia and healthy subjects has been that patients usually perform worse on these tests, thus making the comparison unfair. Critics of this approach argue that it is impossible to say whether the abnormal neurobiology causes deficits in performance or vice versa. To address this criticism, we selected patients who could perform the Wisconsin Card Sorting Test well enough to be matched with comparison subjects. Indeed, previous studies (53–55) have shown that there is a certain percentage of patients with schizophrenia who perform well on the Wisconsin Card Sorting Test. Moreover, to further address the issue of performance and the related neurobiology, we also selected another group of patients who were not capable of performing a working memory task as well as the comparison subjects. The two cohorts of patients allowed us to assess possible correlations between NAA in the dorsolateral prefrontal cortex and activation of the working memory network in the presence or absence of impaired performance. It was interesting that the same pattern of relationships emerged during both working memory tasks, irrespective of whether the patients' performance was normal. This suggests that the relationships reflect the capacity of neurons in the dorsolateral prefrontal cortex to recruit the working memory network and that they are not an epiphenomenon of test score. The fact that task performance was normal in one group of patients during the Wisconsin Card Sorting Test but not in another group during the 2-back test suggests that network capacity, although constrained by the neuronal integrity of the dorsolateral prefrontal cortex, was adequate for the demands of the former condition (the Wisconsin Card Sorting Test) but not for the latter (the N-back task).

Our findings are consistent with and amplify an emerging database implicating an abnormality of prefrontal cortical connectivity in schizophrenia. While we have demonstrated this possibility at the level of functional connectivity, others have reported in vivo and postmortem changes consistent with it. Functional neuroimaging studies have suggested that dorsolateral prefrontal cortex dysfunction and connectivity may be responsible for some of the neuropsychological deficits in schizophrenia (10, 21, 22, 48, 56, 57). Postmortem studies of the prefrontal cortex in schizophrenia have shown diminished neuropil (27), a low number of dendritic spines on layer III pyramidal neurons (30), small layer III neurons (32), abnormal levels of developmental and synaptic proteins such as synaptophysin and growth-associated protein 43 (28), and selective abnormalities in gene expression for glutamate NMDA receptor subunits (58). The evidence that neuronal connections of layer III neurons may be especially affected (32, 33) is particularly relevant to our results as these neurons project to other cortical areas, including those recruited during working memory (1). Consistent with our findings and with this body of literature suggesting abnormal connectivity of the dorsolateral prefrontal cortex in schizophrenia, we have recently reported that the same measure of dorsolateral prefrontal cortex neuronal integrity, i.e., NAA-related signals, predicts both

steady-state (59) and amphetamine-induced (60) subcortical dopamine activity in patients with schizophrenia. Thus, a population of dorsolateral prefrontal cortex neurons identified by low NAA signals may be critical effectors of both the cortical pathophysiology implicated in the cognitive deficits of schizophrenia and the dopamine-related phenomena implicated in treatment with antipsychotic drugs. We have also shown (59) that monkeys with developmental prefrontal pathology induced by neonatal lesions of mesial temporal-limbic structures evince analogous relationships between prefrontal NAA measures and subcortical steady-state and stimulus-induced release of dopamine, further indicating that development of prefrontal neurons and of their connections is a potential mechanism for the determination of these relationships.

It is obvious, however, that since our results were obtained with statistical correlations, they do not intrinsically express a relationship of causality. Therefore, even though the evidence supporting our interpretations is robust, the preceding discussion has to be viewed as conjectural. In fact, another possible interpretation of the present findings is that the NAA measures in the dorsolateral prefrontal cortex reflect a low abundance of axon terminals from other regions, e.g., the thalamus (as NAA is also found in neuronal processes). Indeed, in a previous study of rhesus monkeys (61) we showed that neonatal mesial-temporal limbic lesions can induce NAA deficits in the dorsolateral prefrontal cortex, perhaps reflecting a loss of inputs from the lesioned areas. However, by either scenario, i.e., low afferent input to the dorsolateral prefrontal cortex or low efferent activity of the dorsolateral prefrontal cortex, it is the net effect on the connectivity of dorsolateral prefrontal cortex neurons and other cortical areas that the correlations implicate.

Some further caution in the interpretation of the results of the present study should be considered. The presence of a statistical correlation in one group but not in another could be caused by greater variance in the former than in the latter. However, this was not the case in our two groups of subjects in the Wisconsin Card Sorting Test experiment, who did not have significant variance differences in either the activation or NAA data (analyzed with Hartley F-max, Cochran C, and Bartlett chi-square tests). Moreover, it is conceivable that the correlation between NAA in the dorsolateral prefrontal cortex and activation in the distributed working memory cortical network in the patients could simply be an epiphenomenon of the fact that activation in all the other regions of the network has a high degree of covariance with activation in the dorsolateral prefrontal cortex. However, if this was the case, the same correlations between NAA in the dorsolateral prefrontal cortex and activation in the cortical network would have been evident also in the comparison group, where we found a similar degree of high covariance between activation in the dorsolateral prefrontal cortex and the other regions of the network (data not shown). Since this was not the case, we can assume that the correlations in the patients are not such an epiphenomenon. Another line of evidence against the correlations being an epiphenomenon of the high degree of covariance of the activation of all regions in the working memory cortical network is the specificity of correlations to NAA measures in the dorsolateral prefrontal cortex. In fact, if the correlations were an epiphenomenon of intracortical rCBF relationships, it would be expected that NAA in other cortical regions of the network would show similar relationships with activation in the entire working memory cortical network. However, this also was not the case, since NAA measures in the superior temporal gyrus and anterior cingulate did not show correlations with activation of the working memory cortical network at all.

In conclusion, the data of the present study show potentially unique relationships between pathology of dorsolateral prefrontal cortical neurons and physiological activation of the whole working memory network in patients with schizophrenia. These data are consistent with current speculation focusing on the role played by development of the dorsolateral prefrontal cortex and its connections in the pathophysiology of schizophrenia (31, 62).

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