Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal–thalamic–cerebellar circuitry

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ABSTRACT Patients suffering from schizophrenia display subtle cognitive abnormalities that may reflect a difficulty in rapidly coordinating the steps that occur in a variety of mental activities. Working interactively with the prefrontal cortex, the cerebellum may play a role in coordinating both motor and cognitive performance. This positron-emission tomography study suggests the presence of a prefrontal–thalamic–cerebellar network that is activated when normal subjects recall complex narrative material, but is dysfunctional in schizophrenic patients when they perform the same task. These results support a role for the cerebellum in cognitive functions and suggest that patients with schizophrenia may suffer from a “cognitive dysmetria” due to dysfunctional prefrontal–thalamic–cerebellar circuitry.

Cognitive abnormalities are the hallmark of schizophrenia. Patients with this illness have problems with processing input from the world around them, formulating reactions rapidly, and expressing their responses fluently in either words or emotions. Patients are often said to be “socially awkward,” to have “emotional blunting,” or to display “disorganized thinking.” The abnormalities are subtle, but handicapping. Performance of large-scale functions is intact; just as they walk and talk normally, so too they can listen, respond, converse, read, write, and “remember” normally. But performance may be slower than normal, and careful observation often indicates that they have subtle or mild abnormalities of posture, gait, emotional response and expression, and cognitive performance.

In recent times these abnormalities have often been attributed to the effects of treatment, but even a century ago (long before neuroleptics were developed), patients with schizophrenia were described as physically awkward (1). Recent studies of neuroleptic-naïve first episode patients have confirmed these early observations by documenting that they have a variety of “soft signs,” such as poor performance of rapidly alternating movements (2). Such abnormalities are explicable based on a dysfunction in the neural circuitry that coordinates the interaction between perception, retention, retrieval, and response. A network between the prefrontal cortex and cerebellum, linked through the thalamus, may play a key role in such interaction.

The unifying theme in these observations concerning the signs and symptoms of schizophrenia is the concept of “dysmetria”: the inability to receive and process information rapidly, to retrieve the relevant associated constructs, and to produce a well-modulated and fine-tuned response. Conventionally, dysmetria has been considered to be solely a motor process: the inability to make adjustments as one puts her foot

in the right place while performing a tandem gait or finds the “sweet spot” in the tennis racquet. The cerebellum, a beautiful and complexly foliated “second brain” located just below the cerebrum, contributes substantially to this process. If the cerebellum is a cognitive organ, then an abnormality in it and in its interconnected circuits could lead not only to motor dysmetria, but also to “cognitive dysmetria” (3–7).

We have explored the possibility that patients suffering from schizophrenia manifest a cognitive dysmetria, with abnormalities in the cerebellum and its associated cognitive circuits, by conducting a positron-emission tomography (PET) study using $O^{15}H_2O$ while they perform cognitive tasks. Connectivity between brain regions cannot be conclusively proved by the coactivation of these regions during cognitive task performance, but differences in activation patterns between patients and healthy volunteers in brain regions known to have anatomical connectivity can provide suggestive evidence for dysfunctional circuitry in schizophrenia. We selected two tasks that require monitoring of the retrieval and expression of remembered information, since PET studies have shown that prefrontal regions and the cerebellum are actively engaged during retrieval (8–14). We examined schizophrenic patients and normal volunteers during practiced and novel free recall of complex narrative material (story A and story B from the Wechsler Memory Scale). Complex narrative material was used because it approximates a common “real life” situation. It requires the subject to listen to logically linked information told in a series of sentences, to retain it, to use it by repeating it back, and to monitor the success of this process as they do it. People have to perform this kind of learning and recall task in many types of work, school, and interpersonal situations. People with schizophrenia tend to perform poorly in such situations.

A vexing issue in the use of functional imaging techniques to study the neural substrates of disease processes such as schizophrenia or dementia has been the “chicken-and-egg problem.” That is, patients who suffer from these brain diseases tend to perform less well than healthy volunteers on most cognitive tasks. If their brain blood flow is different from volunteers, is it because they are performing the task poorly or because of a specific dysfunction in the brain that produces a downstream effect of poor task performance? We addressed this problem by using two tasks likely to recruit similar neural components, but varying the difficulty level so that performance would be equivalent to that of healthy volunteers on one occasion (“practiced recall”) and poorer than normal on the other occasion (“novel recall”). This design permitted us to determine whether abnormalities in the brain are intrinsic or secondary to task performance. If a common basic pattern of neural abnormality is observed across both conditions, then it

can be inferred to be due to an intrinsic deficit in the neural circuits normally used for the task.

METHODS

Subjects. Subjects were 13 healthy volunteers recruited from the community and 14 patients suffering from schizophrenia who were evaluated in the Iowa Mental Health Clinical Research Center. The mean age of the volunteers was 28.6 years (± 7.2), and their mean educational achievement was 14.7 years of school (± 1.5); 6 were male and 7 female. The mean age of the patients was 30.7 years (± 11.3) and their mean educational achievement 13.2 (± 2.19); 10 were male and 4 female. Patients were either withdrawn from all medication for a 3-week period prior to study ($n = 11$) or had never been previously treated ($n = 3$), to evaluate neural function without the confounds of drug effects. All patients and controls were right-handed, and all gave written informed consent.

Cognitive Tasks. For the condition referred to as "practiced recall," all subjects were given a training session 1 week before the PET study and a "refresher course" one day before the study, using story A, so that their recall included all 25 items defined as constituting discrete story elements. Thus both patients and controls were able to demonstrate near-perfect recall when they were asked to repeat the narrative aloud during PET data acquisition. For the condition referred to as "novel recall," they were allowed to listen to story B 60 sec before PET data acquisition and then to retell it aloud while being imaged. Responses were tape-recorded and scored by using standard methods. During PET studies the controls recalled 24.3 (± 1.5) items from story A and 13.9 (± 3.3) items from story B, while the patients recalled 22.4 (± 3.3) items and 8.9 (± 5.2) items, respectively. The difference between the two groups is not statistically significant for story A, but is for story B ($t = 2.9$, $P = 0.008$). Both active recall tasks were compared with a reference condition frequently used in other PET studies, lying quietly with eyes closed, sometimes referred to as a "resting baseline," since the brain does not actually rest, and since debriefing indicates that subjects are usually thinking at random about past or future activities, we refer to this condition as random episodic silent thought (REST).

MR and PET Data Acquisition and Image Analysis. Methods for collecting MR and PET data have been previously described, as have the techniques for postacquisition processing and image analysis (12–14). Briefly, the PET data were acquired with a bolus injection of $O^{15}H_2O$ using a General Electric PC4096-plus 15-slice whole body scanner. Arterial sampling was done to obtain an input function for quantitative measurements. Images were acquired in 20 five-second frames. Based on time-activity curves over major cerebral arteries, the eight frames reflecting the 40 sec after bolus transit were summed, and these data were used in subsequent image reconstruction and analysis. Cerebral blood flow was calculated on a voxel-by-voxel basis using the autoradiographic method. Injections were repeated at ≈ 15 -min intervals.

MR scans were obtained for each subject with a standard T1-weighted three-dimensional SPGR sequence on a 1.5 tesla General Electric Signa scanner (TE = 5; TR = 24; flip angle = 40; NEX = 2; FOV = 26; matrix = 256×192 ; slice thickness, 1.5 mm). The quantitative PET blood flow images and MR images were analyzed using the locally developed software package BRAINS (15, 16). MR scans were volume-rendered; the anterior commissure–posterior commissure (AC–PC) line was identified and used to realign the brains of all subjects to a standard position and place each brain in standardized Talairach coordinate space (17). The PET image for each individual was then fit to that individual's MR scan using a surface-fit algorithm (18). Each injection was checked for head movement and individually refit as needed. The MR images from all the subjects were averaged, so that the functional

activity visualized by the PET studies could be localized on coregistered MR and PET images where the MR image represented the "average brain" of the subjects in this study (19, 20). The coregistered images were resampled and simultaneously visualized in all three orthogonal planes.

Statistical Analysis. Specific between-group differences in neural activation were explored by a direct statistical comparison between the patients and the healthy volunteers, using nonparametric statistical techniques that are particularly appropriate to complex between-group comparisons in PET studies (21, 22). Statistical techniques that rely on the General Linear Model for between-group comparisons make many assumptions about the data (e.g., that the variances in patients are the same as in healthy volunteers). Therefore, a randomization analysis was used to conduct statistical tests to compare patients and healthy volunteers on these two tasks. Randomization analysis is a nonparametric statistical technique that makes no assumptions about variance and is not affected by between-group differences in variance. Our specific methods for conducting the randomization analysis have been described elsewhere (22).

We conducted two types of randomization analyses. One type, reported in Table 1, examined the differences between the two groups using an initial subtraction analysis (practiced recall minus REST in patients versus controls, and novel recall minus REST in patients versus controls). Although this analysis can be difficult to interpret because it reflects differences between the two groups in both the conditions being compared, it is not confounded by group differences in head shape or size, since they have been removed by the subtraction. As a check on whether the differences were due to the memory task or to REST, however, we also did randomization comparisons of the two groups for each of the individual conditions with no subtractions. Consistencies across the two comparisons served as a guide in our interpretation of the data, as described below. Interpretation was also guided by direct inspection of the registered images.

The selection of a significance threshold is arbitrary. For the results reported herein, we selected a P value of 0.005. Analyses of PET data from prior studies indicate that the peaks produced through randomization are relatively smaller than those produced by Statistical Parametric Mapping or the Montreal method (23, 24). A P value of 0.005 was selected to produce estimates that were similar to results obtained in our prior studies that used a Montreal method for analysis, since it produced peaks of similar size and magnitude (12–14, 23).

RESULTS AND DISCUSSION

The areas activated in the healthy volunteers by these two tasks have been previously described (13, 14). During both the practiced and the novel task, the controls showed activation of very similar regions (14). The normal controls showed activations in motor speech and memory networks, which are presumed to coordinate their functions interactively. Regions activated by the memory/cognitive component of the task include frontal, temporal, thalamic, and cerebellar regions.

The results of the randomization analysis comparing patients and volunteers are shown in Table 1 and Fig. 1. During the practiced task ("Practiced memory task" in Table 1), in which performance is identical in the two groups, the patients have decreased flow in fronto-thalamic–cerebellar regions, as well as the left motor area, supporting the hypothesis that there is a fundamental deficit in this circuitry in schizophrenia. Fig. 1 shows a randomization map, which visually illustrates the fronto-thalamic–cerebellar decrease in cerebral blood flow in the patients. When the patients and controls were compared for the practiced condition with randomization without subtracting REST, the results were essentially confirmed, with the patients showing decreased flow in the right medial frontal

Table 1. Brain regions showing lower blood flow in schizophrenic patients

Region	x	y	z	Pixels (n)
Practiced memory task				
Left anterior frontal	-10	56	1	207
Right medial frontal	7	29	-21	79
Left frontal operculum	-54	14	-4	50
Left motor	-51	-5	25	802
Left thalamus	-14	-12	-1	403
Midcingulate	-5	-12	36	291
Left superior cerebellum	-21	-71	-17	1769
Right superior cerebellum	18	-69	-12	830
Novel memory task				
Left frontal operculum	-40	21	-5	127
Anterior cingulate	3	23	-8	156
Left anterior temporal	-41	11	-35	608
Right anterior temporal	29	17	-33	465
Right thalamus	6	-24	10	235
Mammillary bodies	-4	-6	-8	187
Left lenticular nucleus	-17	0	8	159
Right lenticular nucleus	29	0	4	142
Left cerebellum	-25	-61	-43	140
Right cerebellum	17	-82	-17	2297
Right cerebellum	27	-84	-35	834
Right cerebellum	30	-54	-36	70

The table shows the location of peaks that were found to be higher in the normal controls, based on between-group comparisons of patients and controls using the statistical technique of randomization. Peaks are identified from the randomization comparison using a region name based on visual inspection of co-registered MR and PET images and the x, y, z Talairach coordinates of the peak. The table lists those peaks that exceed a *P* value of 0.005 and reports the number of contiguous pixels that exceed that threshold.

region, a more lateral right frontal region, the left thalamus, and the left cerebellum.

However, these differences could be due to "ceiling effects;" that is, the task was so well practiced that it was easy for both groups, but easier for the normal volunteers in a way that could not be detected since they were insufficiently challenged in comparison with the patients. This possibility was tested by examining the blood flow patterns of the normal volunteers and patients on the novel task, where differential task performance was observed and ceiling effects were not present. These results for the "Novel memory task" are shown in Table 1. This analysis indicates that fronto-thalamic-cerebellar regions also have decreased blood flow in the patients during the novel recall task. Comparisons between the two groups without subtraction also indicate that the patients have decreased frontal and cerebellar flow, and decreased flow is seen in the thalamus, although it does not reach the preselected statistical threshold. Therefore, these findings can be inferred to reflect a primary neural dysfunction in the prefrontal-thalamic-cerebellar network that is used for on-line information processing.

Additional decreases are seen in the patients during the novel task in the anterior cingulate, mammillary bodies, bilateral anterior temporal regions, and bilateral lenticular nuclei. The anterior temporal regions and mammillary bodies are known to be key components of memory networks, based on PET and lesion studies (8–14, 25–30). Further, the mammillary bodies have a direct reciprocal connectivity with the cerebellum (31). The lenticular nuclei also have established anatomic connectivity with the cerebellum and are a crucial amplifier for its role in higher cognitive functions (32). The relationship of the cingulate to the cerebellum is less well established, but many recent studies indicate it to have a role in memory as well (8–14, 33–35).

These results suggest that the novel task, which is more difficult for both patients and healthy volunteers and does not have a ceiling effect, teases out additional areas of abnormality in schizophrenia. Because task performance was poorer in the patients, one cannot say definitively that this represents a primary neural abnormality rather than a secondary effect of poor performance. Nonetheless, several lines of evidence support the possibility that this difference does reflect a primary abnormality. (i) Evidence from MR, PET, and post-mortem studies have suggested the presence of cingulate and temporal lobe abnormalities in schizophrenia, and our results are consonant with those findings (33, 36–38). (ii) Most of the additional regions that emerge in the novel task are part of the cerebellar circuitry and have a role in cognition. (iii) The patients were clearly engaged in the task and did perform it at acceptable levels, albeit more poorly than the volunteers.

CONCLUSIONS AND IMPLICATIONS

Most of the previous studies of the neural mechanisms of schizophrenia have emphasized dysfunctions in single regions in relation to single symptoms or single tasks (36, 39–43). We propose that this relatively piecemeal strategy should be reappraised and that a more parsimonious one should also be explored: that investigators should attempt to identify fundamental cognitive processes that could account for the diversity of symptoms that occur in schizophrenia. Cognitive dysmetria, a difficulty in coordinating and monitoring the process of retrieving, receiving, processing, and expressing information, is one "candidate cognitive dysfunction" that could explain schizophrenia's myriad symptoms. In a PET experiment requiring the retrieval of information from memory and the monitoring of its expression in language, cognitive dysmetria should express itself as a dysfunction in the circuitry that connects the cerebellum with other memory regions of the brain, particularly those in the prefrontal cortex and temporal lobes, and in the subcortical regions that mediate that circuitry such as the thalamus.

The results of this study provide general support for this strategy and for the concept of cognitive dysmetria, and they suggest clues about its neural mechanisms. Specifically, they provide evidence for a dysfunction in the circuitry that links the cerebellum to the prefrontal cortex, including subcortical regions such as the thalamus, globus pallidus, and mammillary bodies. Since the dysfunctional patterns of blood flow in the cerebellar-thalamic-prefrontal circuit occur in patients during both the practiced and the novel conditions, the results suggest that the primary abnormality is a neural misconnection syndrome and is not secondary to poor task performance.

To our knowledge, this is the first PET study to implicate the cerebellum in schizophrenia, which is an interesting region both phylogenetically and anatomically. The cerebellum is one-third larger in human beings than in nonhuman primates; it shares this characteristic of an enormous phylogenetic increase in size with the prefrontal cortex, with which it also has substantial anatomic connections, suggesting that it could perform both cognitive and motor functions in human beings (3, 4, 6, 44–48). Recent evidence suggests that in human beings the cerebellum plays a major role in higher cognitive functions such as memory (4, 6, 7, 28). It is well suited to function as a massive parallel processor because of its cellular array and its well-established connections to the prefrontal cortex (5, 6, 47, 48). Recent evidence also suggests that the prefrontal cortex plays a key role in both memory encoding and retrieval (8–14, 49). "Working memory," or the ability to hold information in a short-term buffer while mental operations are performed, has also been shown to be a primary function of the granular prefrontal cortex and to be disrupted in schizophrenia (50); presumably the prefrontal cortex and the cerebellum may work in concert to coordinate complex on-line information process-

FIG. 1. The results of the randomization analysis used to identify the specific regions where the schizophrenic patients differed from the normal volunteers are shown. Three orthogonal views are shown in each figure, with transaxial at the *Top*, sagittal in the *Middle*, and coronal on the *Bottom*. Green crosshairs are used to show the location of the slice. Images follow radiological convention and show location as if standing at the foot of the bed (transaxial views) or facing patient (coronal views). The statistical maps of the PET data, showing regions where the two groups differed significantly at a 0.005 level, are superimposed on a composite MR image derived by averaging the MR scans from the subjects. Regions in red/yellow tones indicate lower flow in patients during the practiced recall task, while regions in blue indicate higher flow in patients. Although randomization techniques were used to determine statistical significance, the results are portrayed using the value of the associated *t* statistic, which is shown on the color bar on the right. Two types of maps are provided. The "peak map" (*Left*) shows the small areas where all contiguous voxels exceed the predefined threshold for statistical significance (i.e., 0.005). The "*t* map" (*Right*) shows all voxels in the image and provides a general overview of the landscape of the differences between the two groups. The planes have been chosen to illustrate the location of some of the relevant differences. The statistically significant areas where the patients have decreases in flow include left frontal (transaxial view), left thalamus (transaxial and sagittal views), and bilateral cerebellum (sagittal and coronal views); although the peak map places the thalamic peak at its lateral border and on part of the globus pallidus, the *t* map (in conjunction with inspection of other planes not shown) indicates that it is in fact thalamic.

ing. This study has demonstrated that patients with schizophrenia have a decrement in flow in cerebellar and prefrontal regions during both a practiced and a novel recall task, suggesting that the prefrontal–cerebellar connection may be impaired.

This study also adds to the growing evidence supporting a role for abnormalities in subcortical and midline circuitry in schizophrenia, and it specifically suggests that the thalamus may be dysfunctional (19, 36, 51–57). The thalamus has now been shown in postmortem, MR, and PET studies to be

abnormal in schizophrenia (19, 36, 38, 56). In this particular study, significant thalamic abnormalities were noted on the right for the novel task and on the left for the practiced task. This finding is counter to that predicted by the working model that provided its theoretical background, the Hemisphere Encoding and Retrieval Asymmetry (HERA) model (49), which predicts a reverse pattern: the right frontal cortex, initiating retrieval, should be associated with an activation in the right thalamus, with which it is connected, while the contralateral pattern should be observed for the novel task.

Bilateral thalamic activity was seen at lower thresholds, however, and so this paradoxical result may be a consequence of an over-stringent significance threshold.

This study suggests that schizophrenia is probably not best conceptualized as a disease of a single brain region, but rather a disease involving complex circuits that may display different patterns of disruption that will vary depending on the task. It is consistent with other previous studies suggesting the utility of circuit models (39, 58). In the cognitive tasks examined in this study, a basic abnormality was observed in prefrontal–cerebellar–thalamic circuitry in both conditions, but with specific variations between the novel and the practiced task. These variations in pattern are not due to a generalized decrease in cerebral blood flow in schizophrenia, but rather a disruption in functional or anatomical connectivity. Multiple nodes in the network were found to have decreased flow, which could reflect an injury to a single node or to the interconnections between nodes; these two possibilities cannot be definitively disentangled with the present design, but the consistency of the basic pattern of decreased flow across two different tasks strongly suggests that connectivity of multiple nodes is implicated in schizophrenia. The results point to the importance of examining neural circuits in schizophrenia, and suggest that frontal, subcortical, and cerebellar regions may be a crucial part of its abnormal circuitry (59, 60).

Future studies will be required to determine the extent to which the basic circuit found to be abnormal in novel and practiced recall is common across a variety of cognitive tasks and to further dissect the various components of “cognitive dysmetria” in order to operationalize it and identify its distinctive cognitive properties. The strategy must focus on those specific cognitive operations that are used when a components of a task are monitored sequentially, using measures such as reaction time and the improved temporal resolution of functional MR (fMR) in addition to PET. As with motor dysmetria, the strategy must focus on the specific cognitive operations that guide the appropriate initiation, fluidity, sequencing, and monitoring of cognitive acts to ensure that the desired goal-state is achieved.

The mechanisms producing the abnormal patterns of circuitry cannot be determined from this study, but the findings are consistent with a neurodevelopmental hypothesis. That is, among patients who develop schizophrenia, the brain did not form connections and networks according to the DNA-encoded blueprints that have been phylogenetically determined to be most efficient, but has instead formed misconceptions that are less efficient and perhaps more heterogeneous.

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