Speculation on the Meaning of Cerebral Metabolic Hypofrontality in Schizophrenia

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Abstract

Cerebral metabolic hypofrontality in schizophrenia is a controversial research finding. In this article we discuss some of the issues that fuel this controversy, and we speculate on the neural mechanisms that may be responsible for the finding. Most regional cerebral blood flow (rCBF) studies using radioactive xenon have found hypofrontality; the results of positron emission tomography (PET) studies have been less consistent. Several technical factors are discussed that might contribute to the inconsistencies, including airway artifacts with xenon, limitations of tomography in studying the cortex, and approaches to data analysis. The possibility that hypofrontality is a result of medication is also critically examined. The medication factor is still unclear, but most studies of patients before and after neuroleptic medication find that cerebral metabolism goes up, not down, after treatment. The role of patient behavior and experience during an rCBF or PET procedure is an important variable that has not been adequately controlled in most studies. We suggest that this has been the most important variable in interpreting cerebral metabolic data in schizophrenia. Studies of patients examined during a behavior that normally activates prefrontal cortex have consistently found hypofrontality. One theoretical mechanism that could account for hypofrontality as well as many clinical and research findings in schizophrenia is dysfunction of dopaminergic neural transmission at the level of the prefrontal cortex.

In 1974, Ingvar and Franzen (1974a, 1974b) reported that the distribution of metabolic activity in the cerebral cortex of patients with schizophrenia was different from that seen in normal individuals. Using one of the pioneering techniques in functional brain imaging, they were able to determine the regional cerebral blood flow (rCBF) landscape of the living brain and to observe how this landscape changed during various motor and cognitive behaviors. Since rCBF is determined under most circumstances almost entirely by neuronal activity (Raichle et al. 1976; Siesjo 1984; Kety 1985), they were mapping regional brain function or "work." One of their fundamental findings in normal individuals was that under most test conditions (e.g., during resting and during the performance of cognitive tasks) there was relatively greater blood flow to the prefrontal cortex than to temporal or parietal cortices. In patients with schizophrenia, however, this pattern of relative "hyperfrontality" was attenuated; the patients appeared "hypofrontal" (Ingvar and Franzen 1974a, 1974b; Franzen and Ingvar 1975a, 1975b). Moreover, the more hypofrontal they appeared, the more they were characterized clinically as withdrawn, mute, inattentive, unreachable, etc. (Ingvar and Franzen 1974a; Franzen and Ingvar 1975b).

For reasons that are not entirely clear, the findings of Ingvar and Franzen had little impact on research in schizophrenia until almost 10 years later. Perhaps, their

potential meaning was obscured by the unfamiliarity of the rCBF method. The possibility that they had identified a primary pathophysiological mechanism for some of the most serious features of the illness was rarely discussed in the literature before 1982 (Buchsbaum et al. 1982).

During the past 5 years, the finding of metabolic "hypofrontality" in schizophrenia has become one of the most actively studied and hotly debated neurobiological issues in schizophrenia research. Its appeal is due to the potential clinical-pathophysiological explanation it offers Metabolic hypofrontality may represent direct experimental evidence of a primary neurophysiological mechanism responsible for core schizophrenic symptoms The debate, however, stems from the fact that hypofrontality has not been consistently replicated and from the possibility that it is an artifact or epiphenomenon. In the discussion that follows, we address some of the issues that fuel this controversy and speculate about the neural mechanisms implicated in "hypofrontality" in schizophrenia.

Is Metabolic Hypofrontality a Replicable Finding?

In a recent review of the xenon inhalation rCBF literature on schizophrenia, we concluded that relatively reduced rCBF to prefrontal cortex was a reproducible, albeit inconsistent, finding in schizophrenia research (Berman and Weinberger 1986). The few rCBF studies that have appeared since our review also have found hypofrontality (Chabrol et al 1986, Guenther et al 1986; Geraud et al. 1987)

In a review of studies that used positron emission tomography (PET) to measure glucose or oxygen metabolism, Weinberger and Kleinman (1986) concluded that overall this literature also supported the finding of hypofrontality. The results of studies that have been published since this review have been less consistent (see table 1) While hypofrontality is still found in some studies, the recent majority have failed to make this observation. It appears, therefore, that

Table 1. Position emission tomography (PET) studies published since review by Weinberger and Kleinman (1986)

Study	Sample size	State	Hypofrontality results
Wolkin et al (1985)	10 patients 8 controls	Rest	Reduced absolute prefrontal glucose metabolism
Jernigan et al (1985)	6 patients 6 controls	Auditory vigilance task	No difference in frontal ratio analysis Absolute data not given
Kling et al. (1986)	6 patients 12 controls	Rest	No difference in frontal ratio analysis Absolute data not given
Volkow et al (1986)	4 patients 12 controls	Rest	No difference in absolute frontal glucose metabolism
Early et al (1987)	10 patients 20 controls	Rest	No difference in prefrontal regional cerebral blood flow by ratio analysis Absolute data not given
Gur et al. (1987b)	12 patients 12 controls	Rest	No difference in absolute or relative glucose metabolism
Volkow et al. (1987)	18 patients 12 controls	(1) Rest (2) Eye tracking	Reduced absolute & relative prefrontal glucose metabolism during both conditions
Cohen et al. (1987)	16 patients 27 controls	Auditory vigilance task	Reduced absolute prefrontal glucose metabolism
Kishimoto et al (1987)	20 patients 5 controls	Rest	"Hypofrontal pattern" seen in 6 patients

at issue is not whether metabolic hypofrontality can be found in studies of schizophrenia, but rather what accounts for the inconsistencies.

Is Hypofrontality a Technical Artifact?

To the extent that metabolic hypofrontality has been observed with both the xenon inhalation rCBF method and with PET, a technical artifact is an unlikely explanation for the fundamental finding. These functional brain imaging approaches share very few technical details, and neither method is subject to the important artifacts of the other.

In general, studies employing non-PET rCBF techniques have tended to confirm the original findings of Ingvar and Franzen, while PET studies have been less likely to do so. This raises the possibility that technical and/or procedural differences between techniques might explain the discrepancies. Is it possible, for example, that some artifact unique to the non-PET rCBF method might erroneously make patients appear hypofrontal? The xenon inhalation technique is prone to so-called airway artifact, i.e., spurious elevation in rCBF data due to contamination of the brain radioactivity clearance curves by the high concentration and relatively rapid clearance of radioactivity from the upper respiratory air passages (Obrist et al. 1975). Prefrontal rCBF values are particularly vulnerable to this artifact. If patients with schizophrenia were less prone to this artifact than were normal individuals, they might appear hypofrontal on this basis. While it is difficult to imagine why patients with schizo-

phrenia would be less susceptible to this artifact (do they have less patent sinuses?), studies of rCBF during cognitive activation all but rule out this artifact as an explanation for the increased likelihood of finding hypofrontality with non-PET rCBF methods. As described below, some studies have shown that finding hypofrontality may depend on the cognitive behavior of the subject during the rCBF procedure. It is highly improbable that the risk of airway artifact would be cognitively specific.

Is it possible that some artifact unique to PET studies might contribute to the reduced likelihood of finding hypofrontality with this method? One possibility that has been proposed (Mazziotta et al. 1981) is the problem of so-called partial volume artifact inherent in all tomographic techniques. Since the cortex is only a few millimeters thick, it is represented as only a thin rim on a tomographic section or slice. The metabolic contribution of this rim may be underestimated or diluted because it is averaged along with subjacent subcortical tissues that together fill the volume of a resolution element of the method. The extent to which this problem may limit the sensitivity of PET in studying subtle variations in cortical metabolism has not been determined. It is primarily a theoretical concern at the present time. Since the nontomographic xenon rCBF technique is two dimensional and "views" almost exclusively superficial cortex, it is not subject to this artifact.

While both PET and two-dimensional rCBF methods are valid and sensitive approaches to measuring brain metabolism, there are advantages and disadvantages of each that may also bear on the

research discrepancies. For example, the nontomographic xenon inhalation rCBF technique has limited spatial resolution compared with PET and provides no physiological information about subcortical structures. If hypofrontality were less frequently observed with this method, it might be because of these limitations. However, it is difficult to imagine how these limitations would favor the non-PET method in finding a regional metabolic deficiency.

On the other hand, the non-PET method has the advantages of being noninvasive and of having shorter time resolution than PET studies of glucose metabolism. If the emotional and/or psychological state of the subject affects the distribution of regional brain metabolism, and if this effect could obscure hypofrontality, then noninvasiveness and short time resolution might be important procedural variables that favor the non-PET methods. These procedural considerations may contribute to the fact that PET studies have less consistently found hypofrontality in schizophrenia. The issue of the emotional and behavioral state of the subject during a functional brain imaging procedure and its potential impact on the physiological data is discussed in greater detail below.

One aspect of hypofrontality that has tended to vary between methods is exactly how the concept is defined. Because PET studies generally find large interindividual variance in absolute metabolic values, regional PET metabolic data are usually "normalized" to reduce this variability. Thus, hypofrontality has often been defined on a relative basis; i.e., the regional PET data are expressed as a percentage of

whole brain or hemispheric metabolism The presence or absence of hypofrontality in a PET study that uses this approach to data analysis does not tell us whether there is an absolute reduction in frontal lobe metabolic activity. It is conceivable that a real and clinically meaningful reduction in frontal lobe function and metabolism might exist but be obscured in a relativity analysis by a less clinically important reduction in posterior cortical metabolism It is interesting to note that most PET studies that analyzed absolute metabolic activity tended to find reductions in prefrontal cortex in schizophrenia (Wolkin et al. 1985; Volkow et al. 1987), while those that used only relativity analyses (Widen et al. 1983; Jernigan et al. 1985; Kling et al. 1986; Early et al

1987) most often found no differences between patients and controls. However, the data from the rCBF studies, which have been analyzed in both absolute and relative terms, do not clarify this issue. With the rCBF data, the finding of hypofrontality appears to depend less on which method of analysis is used

In conclusion, it is unlikely that technical artifacts alone explain the inconsistencies in the literature on metabolic hypofrontality in schizophrenia. The impact of "state" phenomena on cerebral physiology seems more critical.

Is Hypofrontality a Neuroleptic Medication Effect?

Several groups of investigators have suggested that hypofrontality

is an effect of neuroleptic medication (Sheppard et al. 1983; Wolkin et al 1985, Early et al. 1987; Volkow et al 1987) Most rCBF and PET studies that found hypofrontality did so in chronic patients who had been receiving antipsychotic medications usually for years Studies of acute patients or those relatively early in the course of their illness have tended not to find hypofrontality (e.g , Sheppard et al. 1983; Widen et al 1983) While some positive studies have examined patients who had been withdrawn from medications and studied in a drug-free state, even these studies have been criticized because patients were typically drug-free for only a few weeks and pharmacological effects of neuroleptics may persist for longer periods. Finally, three PET

Table 2. Studies of prefrontal metabolic effects of neuroleptics

| Study	Sample	Effect of medication
Wolkin et al (1985)	10 patients	Increase in absolute mean prefrontal metabolism after several weeks of standard treatment. Because of slightly greater increase in posterior metabolism, ratio of frontal/posterior decreased
DeLisi et al (1985)	9 patients	No significant change in frontal/posterior ratio after up to 3 years of standard treatment Increase in overall cortical metabolism. Data from prefrontal metabolism not given
Sedvall et al (1985)	10 patients	No change in premotor cortex glucose metabolism after several weeks of sulpiride. Increase in Wernicke's area metabolism Reduction in ratio of premotor/Wernicke's
Berman et al (1986)	9 patients	Slight increase in absolute mean prefrontal activation during prefrontally specific cognitive task after 6 weeks of 0.4 mg/kg haloperidol
Volkow et al (1986)	4 patients	Slight increase in absolute mean prefrontal glucose metabolism 1 hour after 5 mg of thiothixene
Buchsbaum et al (1987)	8 patients	Increase in absolute mean prefrontal glucose metabolism after 3–14 months of standard treatment
Gur et al. (1987c)	12 patients	No change in absolute mean prefrontal glucose metabolism after 3–33 weeks of standard treatment

studies have been published that examined never-medicated patients (Sheppard et al. 1983; Volkow et al. 1986; Early et al. 1987), and none of these found hypofrontality.

Taken on face value, these pieces of evidence raise serious doubts about whether hypofrontality is a primary pathophysiological finding in schizophrenia. However, the data that implicate a medication effect are far from conclusive and run counter to another line of circumstantial evidence that makes medication seem an improbable explanation for hypofrontality. The most compelling argument for a medication effect is based on the three studies of never-medicated patients. Yet, these studies consisted of very small patient samples (six in the case of the study of Sheppard et al., four in the Volkow et al. study, and 10 in the Early et al. study). In contrast are two recent rCBF studies with similarly small samples of never-medicated young patients that did find hypofrontality (Chabrol et. al 1986; Geraud et al. 1987).

If neuroleptic medication is a cause of hypofrontality, it is a very inconsistent one. Indeed, if the rCBF and PET literature are considered together, the likelihood of *not* finding hypofrontality is virtually the same in studies of patients on neuroleptics as it is in studies of patients who were medication-free.

The most compelling evidence against the role of medication is the results of studies that have compared the regional metabolic changes that occur when patients go from the unmedicated to the medicated state. There are seven published studies that have examined these changes (see table 2). In three of the four PET

Figure 1. Comparison of Frontal Index, a ratio of frontal to nonfrontal regional cerebral blood flow (rCBF), in 13 patients during a medication-free (≥ 4 weeks) and a medicated state (6 weeks of 0.4 mg/kg haloperidol)
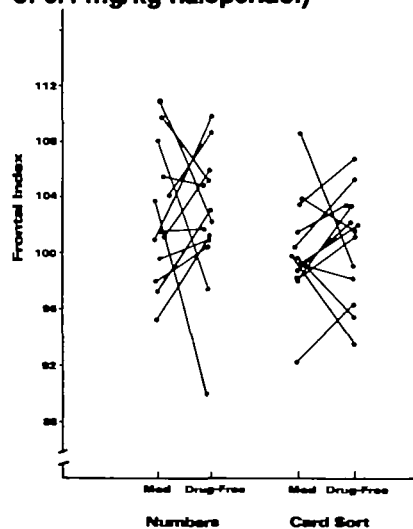
Data are for rCBF during two cognitive tasks: Number Matching and Wisconsin Card Sort.

studies that reported absolute changes in prefrontal glucose metabolism, activity actually increased after treatment. In the other PET study (Gur et al. 1987c), there was virtually no change. In our series of rCBF studies during specific cognitive activation states, the degree of absolute prefrontal activation during the prefrontal specific task (the Wisconsin Card Sort Test) compared with the non-prefrontally specific baseline task (the Number Match Test) was higher in patients treated with neuroleptics (Berman et al. 1986).

Five of the studies of patients on and off medication also reported relative metabolic or rCBF data. Early et al. (1987) cite three of these (DeLisi et al. 1985; Sedvall et al. 1985; Wolkin et al. 1985) as providing evidence for a medication

effect in that each found a weak tendency for the ratio of prefrontal activity to nonprefrontal activity to go down with medication. This interpretation is somewhat misleading, however, as in two of the studies (DeLisi et al. 1985; Wolkin et al. 1985) absolute cortical activity increased after treatment. In the other study, prefrontal metabolism did not change (Sedvall et al. 1985). The ratio appeared to diminish in these reports only because posterior activity increased to a slightly greater degree. Moreover, in the study of Sedvall et al., the ratio that fell slightly was *premotor*/Wernicke's area metabolism, a ratio that provides no information about the effect of medication on *prefrontal* function.

It should also be noted that two other studies reported ratio data and found no effect of medication (Berman et al. 1986; Buchsbaum et al. 1987). Both of these studies employed activation paradigms. In our own series, greater hypofrontality was found with ratio measures after medication, but only during the resting state. The results of our studies and those of others (Gur et al. 1983, 1985; Duara et al. 1987) strongly argue against the use of resting state data as reliable physiological information in neuropsychiatric populations. During the specific cognitive activation states that were the crux of our studies, no consistent medication effect was seen. The data for frontal index (a ratio of frontal to nonfrontal flow) for 13 patients from our original series are shown in figure 1.

Finally, we have studied rCBF during resting and during cognitive activation in patients with Huntington's disease (Weinberger et al. 1988) five of whom had been chronically maintained on low

Figure 2. Comparison of relative prefrontal regional cerebral blood flow (rCBF) in Huntington's patients who were taking and who had never taken neuroleptic medications

HUNTINGTON'S DISEASE
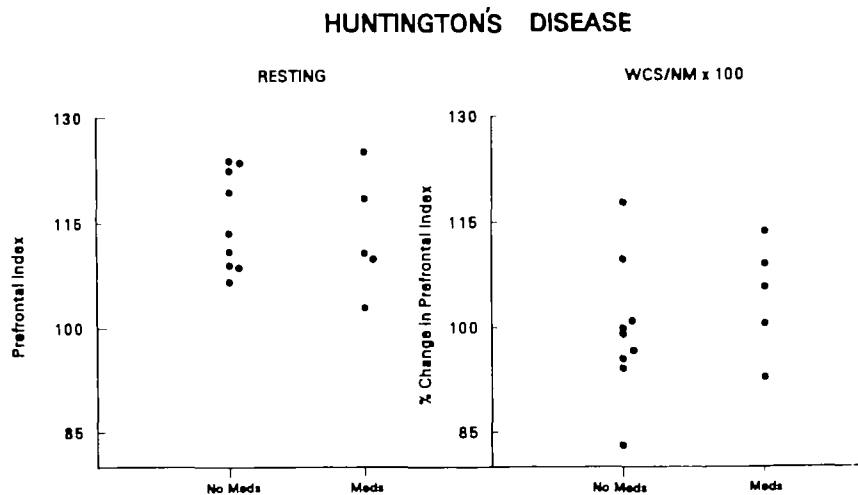
The comparison is during the resting state and during the Wisconsin Card Sort paradigm (see text)

doses of neuroleptic drugs (1-5 mg/day of haloperidol or its equivalent). As seen in figure 2, there was no difference in pre-frontal rCBF, even with ratio data, between neuroleptic-treated and drug-naive patients.

It is interesting to speculate about why treatment with neuro-leptic medication might not consistently produce diminished prefrontal metabolism. Neuroleptics are powerful antipsychotic com-pounds that by blocking post-synaptic neurotransmitter receptors might be expected to turn down postsynaptic activity. In fact, animal experiments are often cited as proof of the effect neuroleptic drugs have in reducing brain glucose metabolism (McCulloch et al. 1982b; Pizzalato et al. 1985). These experiments in rats, however, are not likely to explain the effects seen in humans. The equivalent animal doses were much higher, and glucose metabolism

diminished throughout the brain, even in regions lacking dopamine projections. In other words, the effect probably represented generalized metabolic depression as a result of physiological overdosage.

The data in humans are more consistent with animal research that shows that regional cerebral glucose metabolism correlates primarily with activity in presynaptic terminals (Schwartz et al. 1979). Since dopamine projections to the prefrontal cortex appear to become and to remain overactive following neuroleptic administration (Bannon and Roth 1983), *increased* glucose metabolism in prefrontal cortex might be the expected change following neuro-leptic drug treatment.

In conclusion, there are at present no compelling data to implicate medication status as the primary determinant of hypofron-tality in schizophrenia. More work

is needed, however, before this question can be firmly resolved. It is our view that other state-related variables (especially patient behavior) are more important.

Is Hypofrontality Linked to Patient Behavior?

The studies of Ingvar and Franzen found an association between hypo-frontality and defect or negative symptoms. There has been recent confirmation of this correlation in at least one PET study (Volkow et al. 1987) The implication of this correlation is that hypofrontality might represent a pathophysio-logical correlate of an aspect of schizophrenic behavior and not of schizophrenia, per se This may help explain the inconsistencies in the research literature. If hypo-frontality is behaviorally linked, then it is conceivable that unless patients with the behavior that is most related to hypofrontality are well represented in a study sample, then that study might not report this finding. It is also conceivable that other behaviors might obscure hypofrontality even in someone with the underlying physiological dysfunction, perhaps by altering frontal metabolism through different pathways or by compensating for the deficit that hypofrontality represents.

These possibilities are consistent with the notion that metabolic brain-imaging data represent the sum of a diverse set of cerebral physiological phenomena, some of which are related to the illness while others are related to the behavior and experience of the subject during the procedure Several groups have published data showing that state variables, partic-ularly anxiety, may correlate with PET metabolic data during the resting state (Volkow et al 1987;

Gur et al. 1987b). Gur et al. (1987a) also reported that patients generally felt less anxious about having a noninvasive rCBF study than about undergoing a PET procedure. We have found that in trained psychodramatists simulating in their mind the experience of anxiety, rCBF increased 20 percent over their own relaxed resting baseline values (Weinberger et al. 1984). Geraud et al. (1987) recently published an interesting study in which they found that even medicated patients with chronic schizophrenia, who as a group manifested hypofrontality, could appear not to be hypofrontal during an acute symptomatic exacerbation. There are also a number of reports showing that frontal lobe rCBF varies during the performance of intellectual tasks.

It is not surprising that frontal lobe metabolism may vary as a function of different behaviors and emotional states. The function of the frontal lobe is uniquely complex, and it is involved in many aspects of human cognition and behavior. Not surprisingly, reduced absolute or relative frontal lobe metabolism is not specific to schizophrenia; it has been reported in sleep (Townsend et al. 1973), coma (Deutsch and Eisenberg 1987), Parkinson's disease (Bes et al. 1983), and depression (Buchsbaum et al. 1984). Thus, hypofrontality does not invariably reflect a single physiological process and is unlikely to correlate with only one behavior. It has been proposed that frontal lobe metabolism reflects a hierarchy of functions, some specific to prefrontal mediated behaviors and some related to non-specific "housekeeping" functions such as maintenance of arousal, attention, and mental set (Prohovnik et al. 1980). These ob-

servations and proposals suggest that the way the term "hypofrontality" has been used is misleading. Indeed, "hypofrontality," as discussed in the psychiatric literature, has tended to impute fixity to a physiological measure that by definition is functional and is probably context dependent.

These considerations suggest another interpretation for the inconsistencies in the schizophrenia literature on metabolic hypofrontality. It is conceivable that if the emotional and cognitive behavior of patients during a study are important variables in determining their degree of frontal lobe metabolism, then allowing these parameters to vary freely might result in unreliable data. An effort has been made to control for one contextual variable, i.e., medication status, as discussed above. Other contextual variables, however, including the behavioral, emotional, and cognitive nature of the experience of undergoing an rCBF or PET procedure have been addressed in very few studies.

Most rCBF and PET studies have been performed during the so-called resting state, where subjects lie still and engage in no designated motor or mental activity for anywhere from 10 to 60 minutes. The metabolic correlates of how subjects feel, what they think about, how nervous they are, etc., are not controlled for in this paradigm. In other words, the context of frontal lobe metabolism is not held constant. It is not farfetched to assume that the cognitive and emotional experience of a patient would differ from that of a normal control during one of these procedures and that these experiences might also vary from one testing environment to another. This contextual variability

might be expected to result in considerable variability in the research results.

Only five PET studies attempted to control the subjects' behavior and/or experience during the procedure (Buchsbaum et al. 1984, 1987; Jernigan et al. 1985; Volkow et al. 1987; Cohen et al. 1987). Buchsbaum et al. (1984, 1987) administered mild, continuous superficial pain; Jernigan et al. (1985) had patients engage in a simple auditory vigilance task; Volkow et al. (1987) used a simple visual attention task; and Cohen et al. (1987) had patients perform a simple auditory continuous performance task. It is interesting to note that having subjects experience something explicit during the procedure was not consistent in enhancing the yield of these studies. Both Buchsbaum et al. (1982) and Volkow et al. (1987) had also found similar results using only the resting state. The study of Jernigan et al. (1985) is an essentially negative study, though the small sample size demanded a large group effect. Cohen et al. (1987) did not report resting data. Perhaps, the efforts to control patient behavior in these studies were too limited. Each of the tasks required little more than simple attention and allowed for considerable variation in experience. The stimuli were administered for approximately 30 minutes and the metabolic variations of that period contracted into one "representative" metabolic value. In most cases there were no baseline metabolic data against which the behaviorally linked data might be compared. An analysis based on each individual's change from baseline to the specified behavior might have been more informative. This is also an approach to con-

trolling for idiosyncratic differences in subject experience. Finally, in only one of these studies (Cohen et al 1987) were the normal metabolic correlates of the task determined This last point is particularly critical because in interpreting the results in the patients it is useful to know what neural systems normally subserve the particular behavior or experience

Regional CBF during designated cognitive tasks has been the subject of several studies. In the series of Franzen and Ingvar (1975b), a group of young patients was studied while engaged in the Ravens Progressive Matrices test. An older group of patients had rCBF determined during a simple picture interpretation test. Both groups were reported to show less frontal activation than did controls. In the rCBF series of Gur et al (1983, 1985) patients were studied during two tasks: a verbal analogy test that produced 3 percent activation of the left hemisphere in controls and a line orientation task that produced similarly slight activation of the right hemisphere. While prefrontal rCBF, per se, was not assessed, an anterior/posterior quadrant analysis did not find evidence of hypofrontality during either of the tasks The investigators did not analyze whether the groups differed in the degree to which frontal rCBF changed during the tasks as compared with the resting baseline state.

We have studied rCBF during a variety of cognitive tasks and during several "baseline" conditions In our paradigm, each patient serves as his or her own control to minimize idiosyncratic reactions to the procedure and to reduce interindividual behavioral variance We have completed three activation

paradigms: one involving the Wisconsin Card Sort (WCS) test, a problem-solving task that is thought to assess fairly selectively dorsolateral prefrontal cortical cognitive processes (Weinberger et al 1986, in press b; Berman et al. 1986); one involving a visual continuous performance task, a test of sustained attention (Berman et al. 1986); and one involving Ravens Progressive Matrices, a nonverbal intelligence test that is more demanding than the WCS but does not appear to be a prefrontal type cognitive task (Berman et al., in press). Each activation paradigm involves the experimental task and a simple alert baseline condition that requires matching of numbers or objects or, in the case of the CPT, a simple attentional test. This approach permits us to analyze the cerebral metabolic correlates of a variety of cognitive processes and also to determine the degree to which metabolism increases during a particular task over what it is during the baseline (i e , regional cortical functional "reserve").

In these studies, patients were hypofrontal only during the WCS Also, during the WCS they failed to show prefrontal activation over their baseline, unlike the controls The degree to which patients activated prefrontal cortex during the WCS over baseline predicted their performance on the test. In our original series, we observed this failure to activate during the WCS in both unmedicated and medicated patients. We have recently reproduced this finding in a new sample of unmedicated patients (Weinberger et al , in press b) Prefrontal activity over baseline did not differ between patients and controls during the other cognitive tasks Moreover, the only condition

that produced in normals a significant activation of prefrontal cortex relative to baseline was the WCS.

These results suggest that the degree to which patients appear hypofrontal compared with normal controls during an rCBF procedure depends on whether the controls are engaged in an activity that is normally associated with activation of prefrontal cortex. We suggested that discrepancies in the rCBF and PET literature might be explained by differences in the experience of the controls in different laboratories, in that the more the controls tend to use neural systems related to prefrontal cortex, the more patients are liable to appear hypofrontal (Weinberger and Kleinman 1986). These results suggest that this link between hypofrontality and the subject's behavior and experience best explains the inconsistencies in the literature. In addition, the results suggest that schizophrenia involves physiological dysfunction in at least some of the neural systems that facilitate prefrontal function when there is particular need for it

What Is the Pathophysiological Mechanism of Hypofrontality?

Reduced metabolic activity of prefrontal cortex means either that there is intrinsic cortical pathology that interferes with the function of intrinsic neuronal systems or that there is pathology in the connectivities of prefrontal cortex that affect prefrontal function Most examples of intrinsic prefrontal disease, such as Alzheimer's or Pick's disease, or trauma, etc , are characterized by reduced prefrontal metabolism at rest and during virtually all behavioral conditions that have been examined (Ingvar

and Franzen 1974a). This pattern is not consistent with the bulk of the schizophrenia rCBF and PET data. Nevertheless, there is evidence from computed tomography (CT) (Shelton et al. 1988) and post-mortem anatomical studies (Benes et al. 1986) that subtle prefrontal pathology may be associated with schizophrenia. In our studies (Berman et al. 1987), there was no clear relationship between prefrontal cortical markings on CT and prefrontal rCBF during resting or during cognitive activation.

The rCBF and PET data are more consistent with the possibility that pathology extrinsic to pre-frontal cortex impairs prefrontal function. This model would more easily explain the observation that prefrontal physiological dysfunction is variable and most apparent when there is a need for prefrontally mediated behavior (i.e., cognition). We have found experimental support for this model in a study of the correlations between cerebral ventricular size on CT scan and rCBF during various cognitive tasks (Berman et al. 1987). In this study, ventricular size inversely correlated with relative prefrontal rCBF, but only during the WCS condition when prefrontal metabolic demand is greatest. Since ventricular size in schizophrenia may correlate with pathology in periventricular limbic and diencephalic systems that connect with prefrontal cortex (Weinberger 1987), these data may indicate that the implications of pathology in these regions for cortical function are most profound when prefrontal neural systems are required.

The mechanism by which pathology in subcortical systems affects prefrontal function is unknown. One possibility is that ascending dopaminergic projections

are either disrupted or dysfunctional at the cortical level. This could explain prefrontal hypometabolism in schizophrenia. Activation of the so-called mesocortical dopamine system increases prefrontal glucose metabolism in laboratory animals (McCulloch et al. 1982a). There is also evidence that its activation is keyed to behavioral situations that might be considered important for normal prefrontal function, such as at times of experiential stress (Herman et al. 1982). In a study of patients with Parkinson's disease, we found that prefrontal rCBF during the WCS correlates with performance on the WCS in the same way it does in schizophrenia (Weinberger et al., in press a). Moreover, prefrontal activation in the Parkinson's patients also correlated with typical motor signs of reduced cerebral dopaminergic function. Finally, further evidence for the possibility that hypo-frontality in schizophrenia is a manifestation of mesocortical dopaminergic dysfunction comes from the study of Geraud et al. (1987). They were able to reverse hypofrontality by the administration of the dopaminergic agonist piribedil.

There is at present no direct evidence of mesocortical dopa-minergic hypofunction in schizo-phrenia. Nevertheless, it is an interesting and testable hypothesis. Dopaminergic hypofunction at the level of the prefrontal cortex has been reported to cause subcortical dopaminergic hyperfunction in laboratory animals (Pycock et al. 1980), suggesting a common mech-anism for both defect and psychotic symptoms. Furthermore, the normal ontological patterns of prefrontal cortical function and mesocortical dopaminergic activity have been proposed as possibly key

elements in the onset and course of the illness (Weinberger 1987).

At the least, Ingvar and Franzen's finding of metabolic hypofrontality in schizophrenia has been a heuristically rich research observation. The intriguing possi-bility remains that it is a clue to a primary neurophysiological abnormality in this illness.

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