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Prefrontal Function in Schizophrenia: Confounds and Controversies [and Discussion]

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Prefrontal function in schizophrenia: confounds and controversies

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SUMMARY

A wealth of clinical data indirectly implicate dysfunction of frontal cortex in schizophrenia, including negative symptoms, the pattern of neuropsychological deficits, and abnormal eye movements. Neuroimaging studies have provided direct evidence of frontal, particularly prefrontal, malfunction, but the results have been inconsistent and controversial. The burning question is whether prefrontal hypofunction is a pathophysiological characteristic of schizophrenia *per se* or an artifact of the imaging protocol. In studies of patients at rest, 'hypofrontality' has been an inconsistent finding, probably because resting is physiologically and psychologically variable. Cognitive activation paradigms, especially during working memory tasks, have been reliable in showing prefrontal hypofunction in patients, but these results have been challenged as artifacts of poor performance. Performance differences have been addressed by studying patients and controls matched either for poor performance or for normal performance. The former approach, which has the potential of elucidating the specificity of physiological mechanisms associated with poor performance, has shown that prefrontal activity in patients with schizophrenia differs quantitatively and qualitatively from that of normals and of other patient populations who perform at a comparable level. The latter approach, which tends not to find prefrontal differences between patients and controls, may be selecting out important aspects of the disease by focusing on unaffected neural functions. While there are pitfalls to each approach and no single study can address all the potential phenomenological confounds, overall, the functional neuroimaging database in patients with schizophrenia suggests that prefrontal cognitive deficits are because of prefrontal pathophysiology and not the inverse.

1. INTRODUCTION

The possibility of prefrontal cortex pathology in schizophrenia has been of interest to researchers and clinicians throughout this century. Prior to the early 1970s, evidence of prefrontal involvement consisted primarily of unreliable reports of postmortem anatomical pathology and of interpretations of clinical phenomena and of neuropsychological test results (Zec & Weinberger 1986). The development in the 1960s of *in vivo* regional cerebral blood flow (rCBF) measurement techniques offered a dramatic new approach to studying brain function in health and disease. In 1974 Ingvar & Franzen reported the first of their pioneering series of studies which found that chronic schizophrenic patients had less frontal relative to posterior rCBF when compared with controls, who tended to show the opposite pattern. This finding, which they referred to as 'hypofrontality,' correlated with the severity of symptoms, especially with so-called 'negative symptoms.' Their data presaged the results of a round of studies that were published over the subsequent fifteen years or so the majority of which reported similar findings (Berman & Weinberger 1991).

The relatively consistent results of this early period, however, have not been sustained in recent studies. With the widespread availability of modern tomographic neuroimaging techniques, the study of schizophrenic prefrontal physiology has emerged as a preoccupation of many research centres around the world. As more data have appeared, the literature has become increasingly confused and the consistency of the early results and the interpretation of their meaning have become uncertain. Several prominent emission tomography studies have failed to observe 'hypofrontality' (Ebmeier *et al.* 1993, 1995; Gur *et al.* 1992, 1995), and some studies of patients admitted with acute exacerbations of symptoms have reported 'hyperfrontality' instead (Ebmeier *et al.* 1993; Szechtman *et al.* 1988; Cleghorn *et al.* 1989). While functional neuroimaging studies of patients performing cognitive activation tasks have been more consistent in showing prefrontal hypofunction than have studies performed during the resting state, task associated rCBF data have been challenged as artifacts of performance differences between experimental groups (Ebmeier *et al.* 1995; Gur & Gur 1995; Frith *et al.* 1995). Such inconsistencies and uncertainties have prompted commentaries in the literature about the validity of prefrontal hypofunction in schizophrenia and about the relevance of prefrontal cortex in this illness. A number of important questions have been raised, such as: Is the finding of prefrontal hypofunction in some studies an artifact of chronicity, of drug treatment, or of other illness-related epiphenomena? Are the inconsistencies in the literature explained by differences in the behavioural character-

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istics of patients during the scans, especially with respect to resting versus cognitive activation? Are findings of prefrontal hypofunction during cognitive activation artifacts of differences between patients and controls in performance on the cognitive tasks? In this report, we will address these questions and the broad controversy about frontal, and in particular prefrontal, function in schizophrenia.

2. CLINICAL AND BASIC RESEARCH IMPLICATE PREFRONTAL HYPOFUNCTION IN SCHIZOPHRENIA

The functional neuroimaging data about prefrontal function in schizophrenia do not exist in a research vacuum. Indeed, if there were no neuroimaging data, there would still be considerable indirect and some direct evidence for prefrontal cortical involvement. As Gur & Gur (1995) recently pointed out, the abundance of other data implicating prefrontal cortex in this illness probably contributed to the early enthusiasm for the neuroimaging results. The clearest indirect evidence comes from a wealth of neuropsychological studies showing deficits on tests of attention, of 'executive' functions, and of working memory that have been linked in human and nonhuman primate studies with prefrontal function (Goldman-Rakic 1991; Goldberg & Gold 1995). The neuropsychological deficits themselves have been shown to be independent of chronicity, of ongoing psychotic symptoms, and of treatment (Lawson *et al.* 1988; Liddle 1995; Goldberg *et al.* 1993*a*; Saykin *et al.* 1991). Moreover, the neuropsychological deficits are robust predictors of prognosis, much more so than are psychotic symptoms, and to some degree may be genetic markers of trait liability (Goldberg *et al.* 1993*b*).

Another robust clinical finding in patients with schizophrenia that is linked to abnormal frontal lobe function is a deficit in smooth pursuit eye movements (Holzman 1985). This deficit, which has been observed in almost every clinical study that has examined such eye movements, is modelled in the nonhuman primate by a lesion of the ventral aspect of the frontal eye fields (MacAvoy *et al.* 1991). It has also been shown to be independent of chronicity, of ongoing psychotic symptoms, and of treatment. Other clinical evidence that has been cited as likely to reflect frontal dysfunction includes so-called soft neurological signs on clinical examination, defect symptoms such as poor motivation, flat effect, and poor insight (Weinberger 1988), and findings from recent electrophysiological investigations (Liddle 1995).

Structural neuroimaging studies also have found evidence of pathology of prefrontal cortex. This includes dilated prefrontal sulci (Weinberger *et al.* 1979; Doran *et al.* 1987; Shelton *et al.* 1988) and diminished frontal lobe volume (Breier *et al.* 1992; Andreasen *et al.* 1994), though these anatomical findings have been less consistent than the neuropsychological and eye movement findings. Several postmortem investigations have reported reduced prefrontal cortical thickness (e.g. Benes *et al.* 1991; Selemon *et al.* 1995), though these results also are inconsistent (e.g. Akbarian *et al.* 1993). MRI spectroscopy studies have further implicated prefrontal cortex as a site of pathology, providing evidence of reduced concentrations of N-acetyl aspartate, an intracellular marker of neuronal pathology (Bertolino *et al.* 1996). Numerous postmortem studies describing neurochemical changes in prefrontal cortex have also appeared. Taken together, results from a variety of clinical and basic studies indicate that the functional neuroimaging data about schizophrenia should be examined in a broader context. From the perspective of this broader database, the functional neuroimaging results might be questioned more for the studies that did not find hypofrontality than for the studies that did.

3. HYPOFRONTALITY IS AN INCONSISTENT FINDING IN RESTING STUDIES

The conclusion that hypofrontality is an inconsistent finding in studies of patients with schizophrenia during the so-called resting state is inescapable. In our own series of rCBF studies of patients, whether medicated or medication-free, hypofrontality during rest has either not been observed (Berman *et al.* 1992) or has been seen only with normalized, not absolute, rCBF data and has been much less robust than during cognition (Weinberger *et al.* 1986, 1988*b*; Berman *et al.* 1986). In a recent review of functional neuroimaging studies of rCBF and of glucose utilization, we found that only around 60% of thirty-nine published reports could be interpreted as showing hypofrontality in patients with schizophrenia (Berman & Weinberger 1991). This percent is lower if cognitive activation studies are excluded. The addition of several recent negative resting studies (e.g. Catafau *et al.* 1994; Ebmeier *et al.* 1995; Gur *et al.* 1995) probably further depresses the resting state hypofrontality hit-rate, though positive resting studies also continue to be reported (e.g. Biver *et al.* 1995; Vita *et al.* 1995).

The reasons for the inconsistencies in studies of patients at rest are probably numerous, likely having to do with differences in patient populations, medication status, and study procedures. While each of these confounds may contribute noise to the functional activity data, none of them seem by themselves to reliably explain the discrepancies. Chronic patients, especially those with prominent negative symptoms, are more likely to be 'hypofrontal' at rest (Ingvar & Franzen 1974; Volkow *et al.* 1987; Tamminga *et al.* 1992; Wolkin *et al.* 1992), but some resting studies even of chronic patients with prominent negative symptoms do not report hypofrontality (e.g. Weinberger *et al.* 1986; Gur *et al.* 1987; Ebmeier *et al.* 1995). Antipsychotic medications have been reported to reduce prefrontal rCBF and glucose metabolism in some studies (Bartlett *et al.* 1991; Holcomb *et al.* 1996; Wolkin *et al.* 1996), but the effects of medications also are inconsistent (e.g. Szechtman *et al.* 1988; Bartlett *et al.* 1991; Ebmeier *et al.* 1995) and hypofrontality at rest is not reliably observed even in studies of medicated patients (e.g. Berman *et al.* 1986; Szechtman *et al.* 1988;

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Kawasaki *et al.* 1993; Ebmeier *et al.* 1995; Gur *et al.* 1995).

The technical sophistication of data collection and analysis also varies widely across studies. For example, many of the early positive resting studies were nontomographic and had low spatial resolution (though it could be argued that because of partial volume effects, this limitation would diminish the likelihood of a finding). Some studies only found effects with normalized data (e.g. Buchsbaum *et al.* 1990, 1992; Biver *et al.* 1995), raising questions about whether the abnormality was in the numerator (i.e. prefrontal cortex) or the denominator (e.g. overactive posterior cortex) employed in the normalization procedure. Nevertheless, negative results have also been found with low resolution scanners and normalized rCBF data (e.g. the particular scanner used in the normalized rCBF study of Ebmeier *et al.* (1995) acquires much of the radioactivity counts in a given '15 mm thick' slice from outside that slice).

In our view, the inconsistencies and controversy surrounding the resting hypofrontality data are, to some degree, 'straw men'. They boil down mainly to two issues. The first is conceptual, that is, whether prefrontal function is impaired in schizophrenia. The functional imaging studies of the resting state have not been able to answer this question. The second is methodological, that is, whether the resting state is the appropriate condition under which the first question should be asked. If the clinical data cited above which independently implicate prefrontal dysfunction in schizophrenia are correct, then the resting state is clearly not the appropriate condition.

Why might the resting state be inappropriate to study prefrontal function in patients with schizophrenia? We believe the most likely explanation for this is that the resting state is uncontrollable and inherently variable at both experiential and physiological levels (Weinberger *et al.* 1986; Weinberger & Berman 1988; Andreasen *et al.* 1995). There is abundant evidence that subtle changes in what a subject attends to, thinks about, or even imagines during the resting state will affect the rCBF data. For example, Corbetta *et al.* (1990) showed in normal subjects that posterior cortical rCBF changed significantly depending on which features of a constant visual scene occupied the subjects' attention. Incidental cognitive processing also has been shown to affect rCBF patterns (Frith *et al.* 1995). Kosslyn *et al.* (1995) reported that visual cortical activity changes significantly during eyes-closed visual imagery. Even activation of sensorimotor cortex by a simple somatosensory stimulus can be significantly attenuated if subjects are distracted (Meyer *et al.* 1991). Individual differences in such psychological and cognitive factors that are not controlled during the resting state could obscure a signal that may be a feature of the pathophysiology of an illness. This seems especially likely if the pathophysiological signal is a subtle one and if data are averaged across subjects, as is standard procedure in most emission tomography studies. While this confound concerns any condition, not just the resting state, its potential impact on the group data would probably be greater during the resting state because there is no prescribed behaviour to focus brain activity and provide for a common physiological signal.

In defence of the resting state, the reliability of resting patterns across time has been noted (Gur & Gur 1995). It is unclear what such reliability reflects. Random noise, for example, would be especially reliable over time. Moreover, reliability may reflect insensitivity. This possibility, that some of the methods used in resting studies of patients with schizophrenia are not sensitive enough to detect the subtle differences that characterize such patients, may be particularly relevant for studies that have looked at glucose utilization with fluoro-deoxyglucose (FDG) and at rCBF with static SPECT tracers. The FDG data reflect metabolic information averaged over a long time period (approximately 30 minutes), and thus subtle pathophysiological signals may be obscured by signals related to nonpathological processes that are averaged during the acquisition. This possible limitation of FDG data is illustrated in studies of patients undergoing hypnosis (Grond *et al.* 1995) and of patients with cortical blindness (Bosley *et al.* 1991). In each of these instances, remarkably little has been found in the FDG PET data, though the conditions all involve dramatic deviations from normal awareness. SPECT rCBF tracers have also been shown to be relatively insensitive to subtle changes in cortical activity, probably for different reasons (Crosson *et al.* 1994).

Regardless of whether resting studies are inconsistent because the state itself is, or whether some of the techniques are not sensitive enough to reliably detect subtle effects against a physiologically noisy background, the resting state has not produced clear data in assessing function of prefrontal cortex, or for that matter any brain region, in patients with schizophrenia. Studies of patients during cognitive activation paradigms have been much more consistent, but the results have been challenged as artifacts of poor performance.

4. PREFRONTAL HYPOFUNCTION IS RELIABLY FOUND DURING COGNITIVE ACTIVATION PARADIGMS

We have explored prefrontal function during cognitive tasks in seven separate studies of independent samples of patients with schizophrenia. In all instances, we found that prefrontal function was reduced during cognitive states that enlisted prefrontal activation in normal subjects. Each of these studies involved paradigms that emphasized working memory. Five studies had patients and controls performing an automated version of the Wisconsin card sorting task (WCS) (Berman *et al.* 1986; Weinberger *et al.* 1986, 1988*b*; Berman *et al.* 1992, *vide infra*), one had subjects perform a delayed alternation learning task (Gold *et al.* 1996, data in schizophrenia not published), and one a 'two-back' working memory paradigm (Callicott *et al.* 1996). We demonstrated in these studies that the finding could not be attributed to medication status, as patients were just as likely to be hypofrontal during the tasks whether medicated or medication-free (Berman *et*

al. 1986), and never medicated patients also appeared 'hypofrontal' during such conditions (Callicott *et al.* 1996). This conclusion is supported by other recent studies showing failure of prefrontal activation in medication-naive patients performing analogous tasks (e.g. Rubin *et al.* 1991; Andreasen *et al.* 1992; Catafau *et al.* 1994).

In our earlier review of functional neuroimaging studies of patients with schizophrenia, we noted that approximately 90% of studies performed during a cognitive activation procedure have found 'hypofrontality' (Berman & Weinberger 1991). Over the past five years, the number of activation-type studies has more than doubled, with the percentage of positive results remaining at least as robust. Clearly, during cognitive activation, prefrontal hypofunction is a reliable finding in patients with schizophrenia. The controversy involves the interpretation of the results.

5. POOR TASK PERFORMANCE: DOES IT EXPLAIN HYPOFRONTALITY?

A variety of factors might account for prefrontal hypofunction during cognitive activation in patients with schizophrenia other than pathophysiology of prefrontal cortex. The most problematic include attention, motivation and mental effort, and level of performance. We have addressed the issues of attention, motivation, and mental effort in previous studies and discussions (Berman *et al.* 1986, 1988*a*; Weinberger & Berman 1988; Berman & Weinberger 1991), and therefore, will concentrate herein on the matter of task performance. A prominent criticism of the cognitive activation literature concerns the fact that patients as a group perform poorer than controls on the tasks. Thus, it has been argued that the physiological data, rather than being responsible for the behavioural deficits, are an artifact of such deficits (Frith *et al.* 1995; Gur & Gur 1995; Liddle 1995). Ebmeier *et al.* (1995, p. 452) concluded that the 'poorer performance of 'frontal' activation tasks by patients with schizophrenia is probably sufficient explanation for the difference from controls)'.

The performance issue is a conundrum; a reasonable theoretical case can be made for either the abnormal cognition or the abnormal physiology being the horse that leads the other variable as the cart. In at least three of our studies, we found in patients a significant relationship between prefrontal activity and task performance (Weinberger *et al.* 1986; Goldberg *et al.* 1995, *vide infra*), indicating, at least, that the cart and horse are paradigmatically connected. As emphasized by the critics of this literature, poor performance could conceivably be the horse. On the other hand, if prefrontal pathophysiology is a characteristic of schizophrenia, then prefrontal-type cognitive deficits would be expected to follow as the cart. What do the experimental data suggest is the correct interpretation?

There are several research approaches that have been taken to address the role of performance. One is to study patients with other disorders who perform poorly on the same task. In principal, if the prefrontal physiological deficit found in patients with schizophrenia is an epiphenomenon of poor performance *per se*, then other subjects who perform as poorly should have similar prefrontal function. We have explored this question in patients with Huntington's Disease, who perform as poorly as patients with schizophrenia on the WCS (Weinberger *et al.* 1988*a*; Goldberg *et al.* 1990), in otherwise healthy elderly subjects matched for performance with schizophrenic patients (Esposito *et al.* 1995), and in patients with Down's Syndrome (Berman *et al.* 1988*b*), who perform much more poorly. In none of these studies did the other groups appear hypofrontal. Thus, poor performance *per se* on the WCS does not by itself account for the finding in patients with schizophrenia.

A second approach has been to study patients during tasks that they also perform more poorly than normals, but that do not normally enlist as robust prefrontal activity. Again in principal, if poor performance *per se* explains the hypofrontality data, than patients should appear hypofrontal on any task that they cannot perform as well as normals. In two studies, one of an attention/vigilance task, the continuous performance task (Berman *et al.* 1986), and one of an abstract reasoning intelligence task, Ravens Progressive Matrices (Berman *et al.* 1988*a*), patients who were hypofrontal during the WCS had relatively normal prefrontal function during both of these tasks, even though their performance was well below normal. We proposed that prefrontal function was relatively normal in patients with schizophrenia during these tasks because the tasks depended less on prefrontal activation than did the WCS. This suggested that task-associated hypofrontality related to the frontal demands of the task and presumably to selective neural systems.

A third approach is to match patients and normal controls for level of performance. There are two ways that this has been explored. The first is illustrated by a series of studies from the Hammersmith PET Group, using a cued and paced verbal production ('fluency') task. This group of investigators argues that this task matches performance of patients and controls and thus obviates this potential confound (Frith *et al.* 1995; Liddle 1995). In studies of patients performing this task, which requires them to utter a word of a certain semantic category every five seconds following a visual cue, they produce the same number of words as normals and they show significant prefrontal activation (Frith *et al.* 1995). Does this mean that they do not have a prefrontal functional deficit? Most likely, it means only that the prefrontal activation effect of this task is not different in normals and in patients. The interpretation of these data are confounded by their own set of problems. When patients perform normally on a task, it may mean that the task does not require function from the neural systems that are affected by the disease process. The prefrontal neural functions enlisted during the cued verbal production task may not be the same as those enlisted by tasks such as the WCS. Cognitive activation rCBF studies have demonstrated that many different neuropsychological tasks are associated with activation of prefrontal cortex (Weinberger 1993). Patients with schizophrenia do many things normally, presumably because many

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functional brain systems can perform within normal limits. Thus, tasks that are associated with normal performance, which are generally simple tasks, may not have the specificity (or power) to reveal pathophysiological aspects of schizophrenic brain function. This issue is analogous to the controversy about matching patients with schizophrenia and controls on IQ. Since schizophrenia affects IQ (Goldberg & Gold 1995), selecting for patients with normal IQ, in effect, selects out a potentially important aspect of the illness.

Another problem that can occur with the interpretation of results from paradigms that involve ostensibly normal performance is that all aspects of performance in patients may not be isomorphic with normals. For example, with the cued verbal production task, patients appear to have a delayed reaction time in responding to the cue (R. Dolan, personal communication). This may reflect that they do not occupy the five second intercue interval in the same manner as the normals. The observation that unlike normals who deactivate temporal neocortex, patients activate this region during this task, while possibly reflecting abnormal intracortical function (Dolan *et al.* 1995; Frith *et al.* 1995), might more critically be interpreted as an indication that their minds tend to wander during the intercue interval. Instead of focusing on or preparing for the next response, they are attending to extraneous, perhaps internal, auditory stimuli. These considerations illustrate that the strategy of employing simple tasks that result in some measures of performance being normal in patients is not as straightforward an approach to the question of prefrontal hypofunction in schizophrenia as it may appear. Normal prefrontal rCBF in patients during such a task does not mean that prefrontal function is normal, nor does it mean that the task is performed the same as in normals.

Another approach to matching performance in patients and normals is to find normals who perform as poorly as patients. This approach at least has the potential to answer the question of whether normals and patients fail by the same mechanisms. We have managed to collect WCS rCBF data from groups matched for percent correct on this test (61% for normals and 60% for patients). Patients (mean age 37, range 26–56) and controls (28, range 26–60) underwent PET rCBF scanning during the WCS as previously described (Berman *et al.* 1995). The data, displayed as SPM images in slices through prefrontal cortex (significance threshold is $P < 0.005$), are shown in the figure. This figure illustrates that the normals activate Brodman areas 9 and 46 bilaterally at this level, as well as a part of cingulate cortex. In contrast, the patients, who overall turn on less of prefrontal cortex than the normals, actually activate a different area of prefrontal cortex (that includes area 10), an area that does not correspond to any of the areas activated in normals. The other panels of the figure illustrate that the region of prefrontal cortex activated in the patients appears to be qualitatively the wrong region with respect to predicting better performance. The upper right panel shows that if we look in the normal subjects at the region that is activated in the patients, which normals do not significantly activate, the more normals tend to activate this region, the worse they perform. In the lower right panel we are looking in the patients at the region that is consistently activated in our studies of normals (i.e. areas 9 and 46), but that is not significantly activated in patients; the more patients

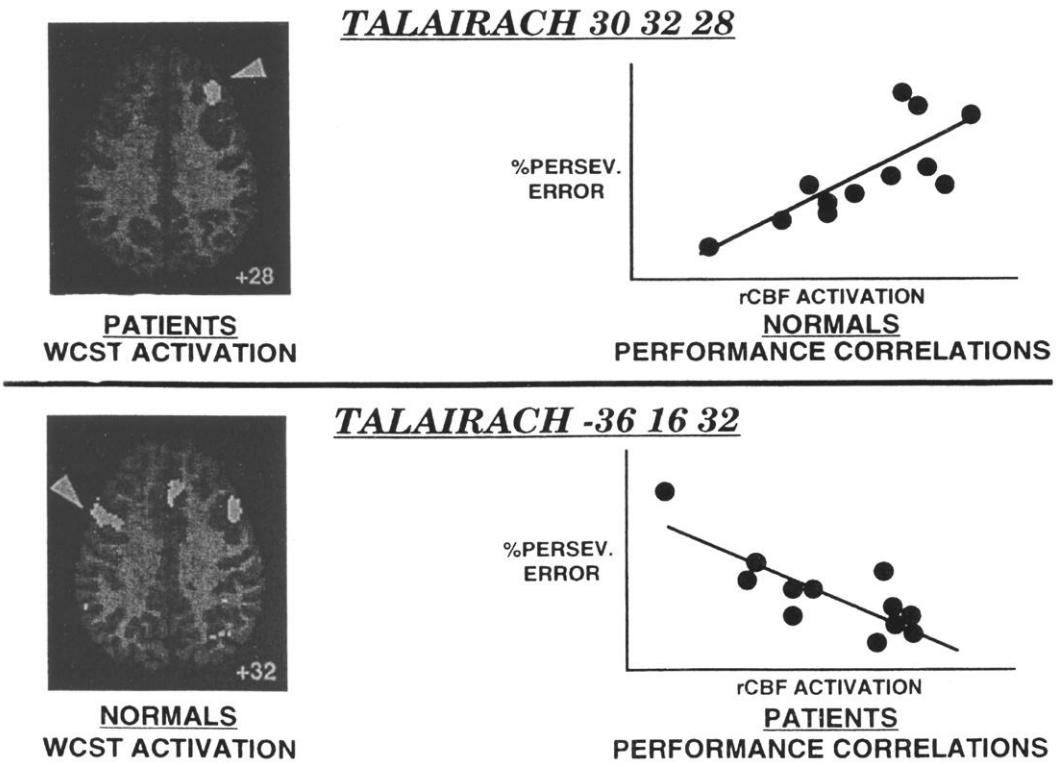

Figure 1. Relationship of performance and prefrontal activation during the WCS in patients and controls. See text for explanation

tend to activate this region the better they do. This analysis illustrates that matching for poor performance has the potential to explore subtle distinctions in the physiological mechanisms that may differentiate the groups. The data suggest that poor performance is not the explanation for poor prefrontal function during the WCS in patients with schizophrenia but that a qualitatively abnormal regional physiological response to the task is. This conclusion is consistent with data from our study of monozygous twins discordant for schizophrenia in which we found that in addition to hypofunction of prefrontal cortex, the affected twin had hyperfunction of hippocampal formation during the WCS (Weinberger *et al.* 1993), a qualitatively abnormal pattern that represents a double dissociation with respect to the normals. Analogous results with the paced verbal production task have recently been described by Friston *et al.* (1996).

6. COMMENT

That the clinical syndrome of schizophrenia involves a deficit in functions of the prefrontal cortex seems highly probable. Prefrontal dysfunction, however, is a nonspecific characteristic of many brain conditions (Weinberger 1993), and precisely what mechanism is associated with schizophrenia and whether it is specific to this disorder are unclear. It is clear, however, that functional neuroimaging studies can be constructed that either show evidence of prefrontal dysfunction or not, depending particularly on the experimental conditions. Studies performed during the resting state have a relatively low probability of revealing prefrontal hypofunction, unless, perhaps, patients are selected for prominent negative symptoms, especially poverty of speech (Liddle 1995). We have found that patients consistently are deficient in prefrontal activity, regardless of their symptomatic profile, during tasks that require working memory and that appear to exceed their capacity for normal task performance. The data from studies of other neurological disorders and of normal subjects who have difficulty with such tasks suggest that the finding in patients with schizophrenia is not the result of their poor performance, but rather is the likely explanation for it. Nevertheless, the possibility that performance differences confound the physiological data cannot be definitively excluded. Comparing patients and controls on simple tasks involving no performance difference (at least on some measures) does not solve the problem, as other at least as problematic confounds are introduced. It is doubtful that any single functional neuroimaging study performed during a cognitive task can by itself answer the 'cart/horse' riddle. Multiple experiments with varied approaches are necessary to approximate the correct answer.

The contrasts between patients with schizophrenia and other groups of subjects who perform poorly on the WCS but activate prefrontal cortex illustrate that the relationships between prefrontal activation during a task and performance on the task are complex. This point is further underscored by a recent study which found that pharmacological ablation of gonadal steroid hormones in normal subjects significantly attenuated prefrontal activation during the WCS without affecting task performance (Berman *et al.* 1995*a*). Thus, activation or no activation (i.e. as defined in a statistical analysis of rCBF data) of the cortical region normally associated with performance of a particular task does not guarantee good or poor performance, respectively. The complexity of the activation-performance relationship may involve multiple factors, including variations in temporal concordances between processing centres, changes in processing efficiency and thus signal to noise, the possible recruitment of alternative neural systems to subserve a particular task, and variations in functional connectivity of the region involved. The anatomical and functional connectivity of prefrontal cortex appears to be an especially important factor in accounting for variations of prefrontal activity in several neurological conditions (Weinberger 1993).

The mechanism of the deficit in prefrontal function in schizophrenia is obscure. Simple models of too little (or too much) activity do not adequately characterize prefrontal function in schizophrenia, any more than a single cognitive task accounts for all prefrontal functions. It has recently been proposed that a more informative perspective is to view prefrontal activity in schizophrenia in relation to activity in other regions (Weinberger & Lipska 1995; Friston *et al.* 1996). For example, as noted above, during the WCS, patients with schizophrenia are hypoactive in prefrontal cortex while they are hyperactive in hippocampus, suggesting an abnormal pattern of correlative intracortical activity. Analogous findings of mesial temporal cortical hyperactivity during the cued verbal production task have been interpreted as evidence that prefrontal cortex fails to inhibit temporolimbic cortex (or is inhibited by it), again implicating an abnormality of intracortical functional connectivity (Frith *et al.* 1995; Friston *et al.* 1996). The results of a study that found a strong correlation between hippocampal volume reduction and prefrontal rCBF during the WCS in patients with schizophrenia is further potential evidence of such an abnormality of cortical interactions (Weinberger *et al.* 1992). Nevertheless, as appealing as this interpretation may be, it is not clear how such a deficit translates into prefrontal hypoactivity during working memory tasks. It is conceivable that the overactivity in nonfrontal areas, rather than being a primary part of the problem in schizophrenic cortex, is an epiphenomena of a primary deficit of prefrontal cortex. Perhaps, in an effort at a solution to the cognitive demands, patients are searching the nexus of neural circuitry to find a substitute for a prefrontal cortex that cannot fit the bill. Future studies will hopefully resolve these uncertainties.

REFERENCES

Akbarian, S., Bunney Jr, W. E., Potkin, S. G., Wigal, S. B., Hagman, J. O., Sandman, C. A. & Jones, E. G. 1993 Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenic implies disturbances of cortical development. *Arch Gen Psychiatry* **50**, 169–177.

Andreasen, N. C., Flashman, L., Flaum, M., Arndt, S., Swayze V, I. I., O'Leary, D. S., Ehrhardt, J. C. & Yuh, W. T. C. 1994 Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. *JAMA* **272**, 1763–1769.

Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G. L., Ponto, L. L. B. & Hichwa, R. D. 1995 Remembering the past: Two facets of episodic memory explored with positron emission tomography. *Am J. Psychiatry* **152**, 1576–1585.

Andreasen, N. C., Rezai, K., Alliger, R., Swayze, V. W., Flaum, M., Kirchner, P., Gohen, G. & O'Leary, D. S. 1992 Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Arch Gen Psychiatry* **49**, 943–958.

Bartlett, E. J., Wolkin, A., Brodie, J. D., Laska, E. M., Wolf, A. P. & Sanfilipo, M. 1991 Importance of pharmacologic control in PET studies: Effects of thiothixene and haloperidol on cerebral glucose utilization in chronic schizophrenia. *Psychiatry Res: Neuroimaging* **40**, 115–124.

Benes, F. M., McSparren, J., Bird, E. D., SanGiovanni, J. P. & Vincent, S. L. 1991 Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry* **48**, 996–1001.

Berman, K. F., Illowsky, B. & Weinberger, D. R. 1988*a* Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity. *Arch Gen Psychiatry* **45**, 616–622.

Berman, K. F., Randolph, C., Gold, J., Goldberg, T. E., Coppola, R., Ostrem, J. L., Carson, R. E., Herscovitch, P. & Weinberger, D. R. 1995*b* Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: A Positron Emission Tomography study. *Neuropsychologia* **33**, 1027–1046.

Berman, K. F., Schapiro, M. B., Friedland, R. P., Rappaport, S. I. & Weinberger, D. R. 1988*b* Regional cortical blood flow during cognitive activation in Down's Syndrome. *Soc Neurosci Abstracts* pp. 10–12.

Berman, K. F., Schmidt, P. J., Ostrem, J. L., Danaceau, M. A., Van Horn, J. D., Esposito, G., Rubinow, D. R. Weinberger, D. R. 1995*a* The effects of gonadal steroid hormones on cognitively-related regional cerebral blood flow: A positron emission tomography study. *J Cereb Blood Flow Metab* **15**, S133.

Berman, K. F., Torrey, E. F., Daniel, D. G. & Weinberger, D. R. 1992 Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. *Arch Gen Psychiatry* **49**, 927–934.

Berman, K. F., Weinberger, D. R. 1991 Functional localization in the brain in schizophrenia. In *American Psychiatric Press Review of Psychiatry Volume* 10 (ed. A. Tasman & S. M. Goldfinger), pp. 24–59. Washington: American Psychiatric Press, Inc.

Berman, K. F., Zec, R. F. & Weinberger, D. R. 1986 Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. II: Role of medication, attention, and mental effort. *Arch Gen Psychiatry* **43**, 126–135.

Bertolino, A., Nawroz, S., Mattay, V. S., Duyn, J. H., Moonen, C. T. W., Barnett, A. S., Frank, J. A., Tedeschi, G. & Weinberger, D. R. 1996 A specific pattern of impaired neuronal metabolism in schizophrenia as assessed by multisclice proton magnetic resonance spectroscopic imaging. *Am. J. Psychiatry*. (In the press.)

Biver, F., Goldman, S., Luxen, A., Delvenne, V., Maertelaer, V. D., Fuente, J. D. L., Mendlewicz, J. & Lotstra, F. 1995 Altered frontostriatal relationship in unmedicated schizophrenic patients. *Psychiatry Res* **61**, 161–171.

Bosley, T. M., Kiyosawa, M., Harbour, R., Zimmerman, R., Savino, P. J., Sergott, R. C., Alavi, A., Reivich, M. 1991 Neuroimaging and positron emission tomography of congenital homonymous hemianopsia. *Am J Ophthalmol* **111**, 413–418.

Breier, A., Buchanan, R. W., Elkashef, A., Munson, R. C., Kirkpatrick, B. & Gellad, F. 1992 Brain morphology and schizophrenia: A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Arch Gen Psychiatry* **49**, 921–926.

Buchsbaum, M. S., Haier R. J., Potkin, S. G., Nuechterlein, K., Bracha, H. S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., Jerabek, P. A., Trenary, M., Tafalla, R., Reynolds, C. & Bunney Jr, W. E. 1992 Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. *Arch Gen Psychiatry* **49**, 935–942.

Buchsbaum, M. S., Nuechterlein, K. H., Haier, R. J., Wu, J., Sicotte, N., Hazlett, E., Asarnow, R., Potkin, S. & Guich, S. 1990 Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. *Br J Psychiatry* **156**, 216–227.

Callicott, J. H., Ramsey, N., Tallent, K., Bertolino, A., Knable, M. B., Coppola, R., Goldberg, T., van Gelderen, P., Mattay, V. K., Frank, J., Moonen, T. W. & Weinberger, D. R. submitted 3-D PRESTO fMRI of a working memory task in schizophrenia. Submitted to *Archives of General Psychiatry*.

Catafau, A. M., Parellada E., Lomeña, F. J., Bernardo, M., Pavía, J., Ros, D., Setoaìn, J. & Gonzalez-Monclús, E. 1994 Prefrontal and temporal blood flow in schizophrenia: Resting and activation technetium-99m-HMPAO SPECT patterns in young neuroleptic-naive patients with acute disease. *J Nucl Med* **35**, 935–941.

Cleghorn, J. M., Garnett, E. S., Nahmias, C., Firnau, G., Brown, G. M., Kaplan, R., Szechtman H. & Szechtman, B. 1989 Increased frontal and reduced parietal glucose metabolism in acute untreated schizophrenia. *Psychiatry Res* **28**, 119–133.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L. & Petersen, S. E. 1990 Attentional modulation of neural processing of shape, color, and velocity in humans. *Science* **248**, 1556–1559.

Crosson, B., Williamson, D. J. G., Shukla, S. S., Honeyman, J. C. & Nadeau, S. E. 1994 A technique to localize activation in the human brain with technetium-99m-HMPAO SPECT: A validation study using visual stimulation. *J Nucl Med* **35**, 755–763.

Dolan, R. J., Fletcher, P., Frith, C. D., Friston, K. J., Frackowiak, R. S.J. & Grasby, P. M. 1995 Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* **378**, 180–182.

Doran, A. R., Boronow, J., Weinberger, D. R., Wolkowitz, O. M., Breier, A. & Pickar, D. 1987 Structural brain pathology in schizophrenia revisited: Prefrontal cortex pathology is inversely correlated with CSF levels of homovanillic acid. *Neuropsychopharmacology* **1**, 25–32.

Ebmeier, K. P., Blackwood, D. H. R., Murray, C., Souza, V., Walker, M., Dougall, N., Moffoot, A. P. R., O'Carroll, R. E. & Goodwin, G. M. 1993 Single-photon emission computed tomography with 99mTc-exametazime in unmedicated schizophrenic patients. *Biol Psychiatry* **33**, 487–495.

Ebmeier, K. P., Lawrie, S. M., Blackwood, D. H. R., Johnstone, E. C. & Goodwin, G. M. 1995 Hypofrontality revisited: A high resolution single photon emission computed tomography study in schizophrenia. *J Neurol Neurosurg Psychiatry* **58**, 452–456.

Esposito, G., Kirkby, B. S., Van Horn, J. D., Weinberger, D. R. & Berman, K. F. 1995 Different pathophysiological mechanisms of altered Wisconsin Card Sort performance

in schizophrenics and elderly normal subjects. *Soc Neurosci Abstracts* **21**, 747.

Friston, K. J., Herold, S., Fletcher, P., Silbersweig, D., Cahill, C., Dolan, R. J., Liddle, P. F., Frackowiak, R. S. J. & Frith, C. D. 1996 Abnormal frontotemporal interactions in patients with schizophrenia. In *Biology of Schizophrenia and Affective Disease* (ed. S. J. Watson), pp. 421–449. London: American Psychiatric Press, Inc.

Frith, C. D., Friston, K. J., Herold, S., Silbersweig, D., Fletcher, P., Cahill, C., Dolan, R. J., Frackowiak, R. S. J. & Liddle, P. F. 1995 Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task: Evidence for a failure of inhibition in left superior temporal cortex. *Br J Psychiatry* **167**, 343–349.

Frith, C. D., Kapur, N., Friston, K. J., Liddle, P. F. & Frackowiak, R. S. J. 1995 Regional cerebral activity associated with the incidental processing of pseudo-words. *Hum Br Map* **3**, 153–160.

Gold, J. M., Berman, K. F., Randolph, C., Goldberg, T. E. & Weinberger, D. R. 1996 PET validation and clinical application of a novel prefrontal task. *Neuropsychology* **10**, 3–10.

Goldberg, T. E., Berman, K. F., Moore, E. & Weinberger, D. R. 1990 rCBF and cognition in Huntington's disease and schizophrenia: A comparison of patients matched for performance on a prefrontal-type task. *Arch Neurol* **47**, 418–422.

Goldberg, T. E. & Gold, J. M. 1995 Neurocognitive deficits in schizophrenia. In *Schizophrenia* (ed. S. R. Hirsch & D. R. Weinberger), pp. 146–162. London: Blackwell.

Goldberg, T. E., Gold, J. M., Greenberg, R., Griffin, S., Schulz, S. C., Pickar, D., Kleinman, J. E. & Weinberger, D. R. 1993*a* Contrasts between patients with affective disorder and patients with schizophrenia on a neuropsychological screening battery. *Am J Psychiatry* **150**, 1355–1362.

Goldberg, T. E., Torrey, E. F., Gold, J. M., Bigelow, L. B., Ragland, R. D., Taylor, E. & Weinberger, D. R. 1995 Genetic risk of neuropsychological impairment in schizophrenia: A study of monozygotic twins discordant and concordant for the disorder. *Schizophr Res* **17**, 77–84.

Goldberg, T. E., Torrey, E. F., Gold, J., Ragland, D., Bigelow, L. B. & Weinberger, D. R. 1993*b* Learning and memory in monozygotic twins discordant for schizophrenia. *Psychol Med* **23**, 71–85.

Goldman-Rakic, P. S. 1991 Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In *Psychopathology and the Brain* (ed. B. J. Carroll & J. E. Barrett), pp. 1–23.

Grönd, M., Pawlik, G., Walter, H., Lesch, O. M. & Heiss, W.-D. 1995 Hypnotic catalepsy-induced changes of regional cerebral glucose metabolism. *Psychiatry Res: Neuroimaging* **61**, 173–179.

Gur, R. C. & Gur, R. E. 1995 Hypofrontality in schizophrenia: RIP. *Lancet* **345**, 1383–1384.

Gur, R. E., Mozley P. D., Resnick,, S. M., Mozley, L. H., Shtasel, D. L., Gallacher, F., Arnold, S. E., Karp, J. S., Alavi, A., Reivich, M. & Gur, R. C. 1995 Resting cerebral glucose metabolism in first-episode and previously treated patients with schizophrenia relates to clinical features. *Arch Gen Psychiatry* **52**, 657–667.

Gur R. E., Resnick S. M., Alavi, A., Gur, R. C., Caroff, S., Dann R., Silver F. L., Saykin A. J., Chawluk, J. B., Kushner, M. & Reivich, M. 1989 Regional brain function in schizophrenia. I. A positron emission tomography study. *Arch Gen Psychiatry* **44**, 119–125.

Holcomb, H. H., Cascella, N. G., Thaker, G. K., Medoff, D. R., Dannals, R. F. and Tamminga, C. A. 1996 Functional sites of neuroleptic drug action in the human brain: PET/FDG studies with and without haloperidol. *Am J Psychiatry* **153**, 41–49.

Holzman, P. S. 1985 Eye movement dysfunctions and psychosis. *Int Rev Neurobiol* **77**, 179–205.

Ingvar, D. H. & Franzen, G. 1974 Distribution of cerebral activity in chronic schizophrenia. *Lancet* **2**, 1484–1486.

Kawasaki, Y., Maeda, Y., Suzuki, M., Urata, K., Higashima, M., Kiba, K., Yamaguchi, N., Matsuda, H. & Hisada, K. 1993 SPECT analysis of regional cerebral blood flow changes in patients with schizophrenia during the Wisconsin Card Sorting test. *Schizophr Res* **10**, 109–116.

Kosslyn, S. M., Thompson, W. L., Kim, I. J. & Alpert, N. M. 1995 Topographical representation of mental images in primary visual cortex. *Nature* **378**, 496–498.

Lawson, W. B., Waldman, I. N. & Weinberger, D. R. 1988 Schizophrenic dementia: Clinical and CT correlates. *J Nerv Ment Dis* **176**, 207–212.

Liddle, P. F. 1995 Brain imaging. In *Schizophrenia* (ed. S. R. Hirsch & D. R. Weinberger), pp. 425–439. London: Blackwell.

MacAvoy, M. G., Bruce, C. J. & Gottlieb, J. P. 1991 Smooth pursuit eye movement representation in the primate frontal eyefield. *Cereb Cortex* **1**, 95–102.

Meyer, E., Ferguson, S. S. G., Zatorre, R. J., Alivisatos, B., Marrett, S., Evans, A. C. & Hakim, A. M. 1991 Attention modulates somatosensory cerebral blood flow response to vibrotactile stimulation as measured by positron emission tomography. *Ann Neurol* **29**, 440–443.

Rubin, P., Holm, S., Friberg, L., Videbeck, P., Andersen, H. S., Bendsen, B. B., Stromso, N., Larsen, J. K., Lassen, N. A. & Hemmingsen, R. 1991 Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform disorder: A regional cerebral blood flow study. *Arch Gen Psychiatry* **48**, 987–995.

Saykin, J. A., Gur, R. C., Gur, R. E., Mozley, D., Mozley, L. G., Resnick, S. M., Kester, B. & Stafiniak, P. 1991 Neuropsychological function in schizophrenia: Selective impairment in memory and learning. *Arch Gen Psychiatry* **48**, 618–624.

Selemon, L. D., Rajkowska, G. & Goldman-Rakic, P. S. 1995 Abnormally high neuronal density in the schizophrenic cortex: A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry* **52**, 805–818.

Shelton, R. C., Doran, A. R., Pickar, D. & Weinberger, D. R. 1988 Cerebral structural pathology in schizophrenia. Evidence for a selective prefrontal cortical deficit. *Am J Psychiatry* **145**, 154–163.

Szechtman, H., Nahmias, C., Garnett, S., Firnau, G., Brown, G. M., Kaplan, R. D. & Cleghorn, J. M. 1988 Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Arch Gen Psychiatry* **45**, 523–532.

Tamminga, C. A., Thaker, G. K., Buchanan, R., Kirkpatrick, B., Alphs, L. D., Chase, T. N. & Carpenter, W. T. 1992 Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch Gen Psychiatry* **49**, 522–530.

Vita, A., Bressi, S., Perani, D., Invernizzi, G., Giobbio, G. M., Dieci, M., Barbarini, M., Sole A. D. & Fazio, F. 1995 High-resolution SPECT study of regional cerebral blood flow in drug-free and drug-naive schizophrenic patients. *Am J Psychiatry* **152**, 876–882.

Volkow, N. D., Wolf, A. P., Gelder, P. V., Brodie, J. D., Overall, J. E., Cancro, R. & Gomez-Mont, F. 1987 Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry* **144**, 151–158.

Weinberger, D. R. 1988 Schizophrenia and the frontal lobes. *Trends Neurosci* **11**, 367–370.
Weinberger, D. R. 1993 A connectionist approach to the prefrontal cortex. *J Neuropsych Clin Neurosci* **5**, 241–253.
Weinberger, D. R. & Berman, K. F. 1988 Speculation on the meaning of cerebral metabolic 'hypofrontality' in schizophrenia. *Schizophr Bull* **14**, 157–168.
Weinberger, D. R., Berman, K. F., Iadarola, M., Driesen, N., & Zec, R. F. 1988*a* *Prefrontal cortical blood flow and cognitive function in Huntington's Disease. J Neurol Neurosurg Psychiatry* **51**, 94–104.
Weinberger, D. R., Berman, K. F. & Illowsky, B. 1988*b* Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. *Arch Gen Psychiatry* **45**, 609–615.
Weinberger, D. R., Berman, K. F., Ostrem, J. L., Abi-Dargham, A. & Torrey, E. F. 1993 Disorganization of prefrontal-hippocampal connectivity in schizophrenia: A PET studies of discordant MZ twins. *Soc Neurosci Abstracts* **19**, 7.
Weinberger, D. R., Berman, K. F., Suddath, R. & Torrey, E. F. 1992 Evidence for dysfunction of a prefrontal-limbic network in schizophrenia: An MRI and rCBF study of discordant monozygotic twins. *Am J Psychiatry* **149**, 890–897.
Weinberger, D. R., Berman, K. F. & Zec, R. F. 1986 Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. I: Regional cerebral blood flow (rCBF) evidence. *Arch Gen Psychiatry* **43**, 114–125.
Weinberger, D. R. Lipska, B. K. 1995 Cortical maldevelopment, anti-psychotic drugs, and schizophrenia: A search for common ground. *Schizophr Res* **16**, 87–110.
Weinberger, D. R., Torrey, E. F., Neophytides, A. & Wyatt, R. J. 1979 Structural abnormalities of the cerebral cortex in chronic schizophrenia. *Arch Gen Psychiatry* **36**, 935–939.
Wolkin, A., Sanfilipo, M., Duncan, E., Angrist, B., Wolf, A. P., Cooper, T. B., Brodie, J. D., Laska, E. & Rotrosen, J. P. 1996 Blunted change in cerebral glucose utilization after haloperidol treatment in schizophrenic patients with prominent negative symptoms. *Am J Psychiatry* **153**, 346–354.
Wolkin, A., Sanfilipo, M., Wolf, A. P., Angrist, B., Brodie, J. D. & Rotrosen, J. 1992 Negative symptoms and hypofrontality in chronic schizophrenia. *Arch Gen Psychiatry* **49**, 959–965.
Zec, R. F. & Weinberger D. R. 1986 Brain areas implicated in Schizophrenia. In *The Neurology of Schizophrenia* (ed. H. A. Nasrallah & D. R. Weinberger), pp. 175–206. Amsterdam: Elsevier N Holland.

Discussion

C. Frith (*Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, WC1N, 3BG*). There are two major problems associated with the interpretation of neuroimaging studies in which groups are compared. The first is a technical problem concerned with parameters like response rate. The second is a conceptual problem concerned with the quality of performance. PET is an integrative technique. If a subject moves his hand twice as often in one scan than another then there will be roughly twice as much activity in the motor system (Fox & Raichle 1985, *Ann. Neurol.* **17**, 303). It is important to equate response rate between groups in order to eliminate this source of difference in activity. However, equating response rate does not eliminate differences in task performance. In our cued word generation task (Frith *et al.* 1995, *Br. J. Psychiat.* **167**, 343–349) there was a longer interval betweem cue and response for the patients than for the controls. This relates to the major conceptual problem which has bedeviled schizophrenia research for decades and makes the interpretation of neroimaging studies especially problematic. Since most patients perform most tasks badly it is very difficult to pin point specific cognitive deficits. In the context of neuroimaging, if the patients are performing differently (slower responses, more errors etc.) it is very difficult to pin point the critical difference in activity. Another approach would be to equate subjective difficulty across groups (Oltmanns & Neale 1975, *J. Abn. Psychol.* **84**, 205–209). This would mean that the schizophrenic patients performed what was in absolute terms an easier task. This approach would bring with it another set of problems. The issue of the right way to compare groups is yet to be resolved. I believe we need to try many different approaches in order to obtain converging evidence.

C. Frith (*Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, WC1N, 3BG*). How would you account for an identical pattern of performance on the Wisconsin card sorting test and yet a completely different pattern of physiology following treatment with the gonadal steroid blocker lupron? Surely it should be possible to provide an explanation of what the subjects are doing at the cognitive level which matches the physiology? Can you show that the subjects were performing the Wisconsin card sorting test in a different way whilst on lupron?

D. R. Weinberger. Dr Frith's question gets to heart of the mystery in the hormone data. It is not easily answered. We trained subjects prior to each of the scan sessions so that the neuropsychological task would be overpractised and overlearned. This was done to minimize any systematic performance differences that might exist across hormonal conditions and that might, *per se*, confound interpretation of the neurophysiological data. Because we took this approach, the study probably had limited capability to detect what may be subtle changes in cognitive style or ability. In fact, the subjects performed very well during each treatment phase. It is tempting to conclude that, in the face of a physiologically perturbed frontal lobe (i.e. the lupron condition), this overlearning enabled neural mechanisms other than the primary ones typically used for the task – i.e. secondary mechanisms that may have varied somewhat between individuals – to carry out the task. In other words, the neural circuitry recruited by the Wisconsin card sorting test (including the portion of the frontal cortex utilized) may have been similar from woman to woman during hormone replacement (thus, allowing rCBF changes in these common areas to reach significance in group average statistics), but while taking lupron the frontal lobe areas used may have differed from woman to woman (thus, cancelling out in group averaging). Because our results were derived from statistical averaging across the group, no conclusions can be reached about the activation patterns of individual subjects.