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CRITICAL REVIEW

Schizophrenia and the frontal brain: A quantitative review

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Abstract

Structural and physiological frontal brain system deficits in patients with schizophrenia are reviewed quantitatively. We report effect sizes from studies since 1980 that used structural (CT, MRI), and functional (PET) neuroimaging methods. We found both literatures to be distinguished by heterogeneity whereby most patients show normative frontal function and structure, a minority shows diminished values and some patients demonstrate augmented function and structure rather than deficit. The average magnitude of difference between patients and controls is generally too modest to support the idea that frontal brain dysfunction is a necessary component of schizophrenia. This modesty is most apparent in average effects obtained for frontal brain volume ($M = -.36$), left frontal brain volume ($M = -.16$), frontal resting metabolism, and blood flow ($M = -.64$). Effect sizes of this magnitude imply that schizophrenia and control distributions overlap by as much as 88% and no less than about 60% on frontal brain measures. It is only when behavioral measures are employed as activation tasks during frontal blood flow and metabolism studies, that average effect sizes rise in magnitude to indicate patient–control distribution overlaps that are less than 50%. Overall, the findings are hard to incorporate within single disease models that propose major involvement of the frontal system, at least at the degree of resolution obtained with current imaging technology. (*JINS*, 1999, *5*, 556–566.)

Keywords: Schizophrenia, Frontal lobes, Neuroimaging, Review

INTRODUCTION

Over the past two decades, evidence from neurobiological studies has revived interest in schizophrenia as a disease that arises, at least in part, from the frontal lobes of the brain (Franzen & Ingvar, 1975; Levin, 1984; Randolph et al., 1993; Seidman, 1983; Taylor, 1995; Weinberger, 1984, 1988). That is, frontal-executive problems observed in patients with schizophrenia and in patients with frontal lobe damage include poor planning, aspontaneity, mental rigidity, and impaired social judgment (Benson & Miller, 1997; Damasio & Anderson, 1993; Stuss et al., 1997; Stuss & Benson, 1984, 1986). While the phenomenologic similarity between some features of patients with schizophrenia and of patients with prefrontal injury is circumstantial evidence of prefrontal dysfunction in the former case, it is not direct and certainly not conclusive evidence (Weinberger et al., 1991). Nevertheless, the availability of *in vivo* anatomic techniques during the 1970s such as computerized tomography (CT) and more recently, magnetic resonance (MRI) and positron emission tomography (PET) have been applied to the problem of finding evidence of abnormal frontal structure and physiology in the illness (Raz & Raz, 1990; Sedvall, 1992; Weinberger et al., 1986). But to what extent is the prefrontal brain system really defective in schizophrenia?

The accumulated literature has generated support for the frontal-executive hypothesis in schizophrenia in the form of statistically significant patient and control group differences. This evidence has been reviewed by several researchers (e.g., Berman et al., 1986; Goldman-Rakic & Selemon, 1997; McKenna & Chua, 1995; Randolph et al., 1993; Velakoulis & Pantelis, 1996). These reviews, however, do not reveal the magnitude of frontal deficit in accumulated CT, MRI, and PET studies of patients with schizophrenia. That is, traditional narrative reviews conflate statistically significant group differences with evidence for frontal dysfunction and do not give due consideration to the magnitude of such differences. Thus, although some interpretations of the literature suggest frontal impairment in many patients, the

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strength and consistency of this evidence has not been evaluated and synthesized quantitatively.

Estimates of deficit magnitude require the quantitative methods of research synthesis provided by meta-analysis (Zakzanis, 1998a). For example, the magnitude, in standard deviation units, of schizophrenia–control group differences in neurocognitive function was addressed recently in a quantitative review of the published literature (see Heinrichs & Zakzanis, 1998). We found a moderately large and reliable impairment of Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) and word fluency (Benton & Hamsher, 1989) performance in schizophrenia samples. The average magnitude of effect size, however, suggested that a substantial proportion of any given schizophrenia sample, perhaps 50%, will be indistinguishable from healthy controls. This may reflect the recent surge of evidence that has found a subgroup of patients with schizophrenia that produce normal results on a variety of neuropsychological tests (e.g., Heaton & Palmer, 1998; Heinrichs & Awad, 1993; Heinrichs et al., 1997; Palmer et al., 1997). Yet cognitive tests are relatively indirect measures of frontal brain system integrity (Freedman, 1984; Lezak, 1995; Shallice & Burgess, 1991), and it is important to characterize further the magnitude of impairment of the frontal system in schizophrenia with neuroimaging measures that are indeed more direct indicators of frontal brain system function and structure.

Accordingly, we conducted a quantitative review of the imaging literature using meta-analytic methodology. Neuroimaging methods considered for our review included structural MRI and CT, which are noninvasive techniques for measuring the anatomy of the brain. MRI allows for an image of higher resolution than CT but both have been applied to measuring frontal brain area and volume in schizophrenia (see Frackowiak, 1997; Kertesz, 1994; Nasrallah & Weinberger, 1986). Spectroscopic and functional MRI remain in their infancy as research tools in schizophrenia and therefore this literature was not reviewed because of an insufficient number of primary studies of the frontal lobes in schizophrenia. Also reviewed were functional neuroimaging findings that offer the advantage of physiological rather than structural anatomical imaging of the frontal area (see Frackowiak, 1997; Thatcher, 1994). The most frequently indexed aspects of physiological function in schizophrenia include glucose metabolism and blood flow as measured with PET and rCBF by xenon inhalation which were all tracked in our literature review. We did not review single photon emission computed tomography (SPECT) studies of the frontal lobes in schizophrenia because of the poorer resolution obtained with this instrumentation (see Ketonen & Berg, 1997). Primary studies utilizing [^{15}O]PET instrumentation were also not collected as this method of radiology has yet to be quantitatively applied to schizophrenia research.

Several broad questions were formulated to guide our analyses:

1. Does neuroimaging data provide reliable evidence of frontal cerebral impairment in schizophrenia?
2. What is the average magnitude of difference between patients and healthy controls?
3. Do structural and functional neuroimaging measures of the frontal system vary in their sensitivity to schizophrenic illness and to what extent do technical differences between scanners and methods vary with effect sizes?
4. Do activation challenge studies yield larger effects than resting studies?
5. Is there more involvement from left frontal cortex than right or bilateral areas?
6. Are there relations between frontal brain system impairment and clinical and demographic attributes of patients and controls?

Hence, the goal of this review was to evaluate the validity of the frontal-executive hypothesis of schizophrenia by determining the consistency, strength, and sensitivity of structural and functional neuroimaging findings.

METHODS

Meta-analysis

We employed standard meta-analytic techniques to our review of the neuroimaging literature in schizophrenia (see Cooper & Hedges, 1994; Hedges & Olkin, 1985; Rosenthal, 1991, 1995). In addition to solving problems with traditional narrative reviews (see Wolf, 1986), meta-analysis provides tools for the analysis of magnitude. Magnitude can be indexed with the effect size estimate *d* that is meant to reflect the degree to which the dependent variable is present in the sample group or the degree to which the null hypothesis is false (Cohen, 1988). In mathematical terms, *d* is the difference between patient and control means calibrated in pooled standard deviation units. Eligible research studies comprising a common dependent variable and statistics that can be transformed into effect sizes are viewed as a population to be systematically sampled and surveyed. Individual study results (typically means and standard deviations from each group) and moderator variables (e.g., education, duration of disease, percent male, age) are then abstracted, quantified and coded, and assembled into a database, which is statistically analyzed (Lipsey & Wilson, 1993). The main statistic presented in a meta-analysis is the mean effect size, which is meant to reflect the average individual effect size across the sample of studies included in the synthesis. Moderator variables are then correlated to the effect size in order to tease out relationships of participant characteristics that may influence the magnitude of the size of effect between the groups being compared. Moreover, the effect size can then be transformed into a nonoverlap percentage (*U*) using Cohen's (1988) idealized distributions that can be used to indicate potential clinical markers for a disease and hence, aid in the differential diagnosis of neurologic and psychiat-

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ric disease (see Zakzanis, 1998a; Zakzanis et al., 1999). The *U* statistic represents the degree of nonoverlap associated with *d* and the distribution of scores between groups (Cohen, 1988). As in our previous review (see Heinrichs & Zakzanis, 1998), we converted the *U* statistic to represent the degree of overlap by subtracting the nonoverlap from 100. Where appropriate, this hypothetical overlap statistic (OL%; overlap percentage) will be mentioned to aid interpretation of the data. Accordingly, the OL% statistic used here represents the degree of overlap between patients with schizophrenia and normal control participants in the distributions of structural and physiological measures of the frontal lobes.

Finally, it should be noted that statistical analysis of meta-analytic studies is not entirely uncontroversial (see Hunter & Schmidt, 1990). A problem with any meta-analytic review of the literature is that primary studies vary in sample size, and that independent variables are not uncorrelated. As Van Horn and McManus (1992) did, we have used a correlational analysis to assess the independent effects of moderator variables, and have made no attempt to weight the various studies according to their sample sizes. In so doing, we are also aware of the problem emphasized by Hunter and Schmidt (1990, p. 86) that in examining meta-analytic data for effects of moderator variables the crucial characteristic is the number of studies and not the number of participants, which paradoxically can sometimes mean that their statistical power is surprisingly low, despite apparently large participant numbers (Van Horn & McManus, 1992). In using univariate and multivariate analysis of studies we have followed Van Horn and McManus (1992) in not attempting to take any account of the differing sample sizes in studies, since despite the concerns of Hedges and Olkin (1985), we have also accepted the argument of Hunter and Schmidt (1990; p. 408) that such problems pale into insignificance in comparison with the problems posed by low power in such studies. In assessing the potential effects of moderator variables we have therefore used unweighted population estimates from individual studies (see Van Horn & McManus, 1990).

Literature Search

We began our review of the literature by conducting a manual search through the volumes of pertinent journals for a topic year by year as recommended by Cooper and Hedges (1994). This was done with every issue for the following journals: *American Journal of Psychiatry*; *Archives of General Psychiatry*; *Biological Psychiatry*; *Brain*; *British Journal of Psychiatry*; *Journal of Abnormal Psychology; Journal of Nervous and Mental Disease*; *Journal of the International Neuropsychological Society*; *Neuropsychology*; *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*; *Neuropsychopharmacology*; *Psychiatry Research*; *Schizophrenia Bulletin*; *Schizophrenia Research*. To reduce the likelihood that bias was involved in the manual search outcome we also located potential studies by conducting a computer based search using the *PsychInfo* and *Medline* databases. The key words used in the database search were "schizophrenia" with independent matched searches with the key word(s) "PET," "positron emission tomography," "MRI," "magnetic resonance," "CT," "computed tomography," "CAT," "computed axial tomography," "NMRI," "nuclear magnetic resonance," "functional magnetic resonance," "brain metabolism," "blood flow," "neuropathology," "neuroimaging," "imaging," "executive," "frontal lobes," "prefrontal cortex," and "frontal-executive." The studies located by the computer search were limited to published English written studies and dissertations. Studies were obtained at two large Canadian Universities and through interlibrary loan.

Study Inclusion Criteria

Articles were included if they met the following criteria: publication between 1980 and 1997; research designs with a control group comprising healthy participants; study statistics convertible to effect size *d* (e.g., means, standard deviations, *F*, *t*, *X*; see Wolf, 1986). Pre-1980 articles were not gathered in keeping with the introduction and use of more systematic and reliable diagnostic criteria for schizophrenia (e.g., DSM–III) that roughly corresponded to this cut-off criterion. If these criteria were met, the article was then assessed for two further criteria. First, patients with schizophrenia must have met diagnostic criteria for either the Diagnostic and Statistical Manual of Mental Disorders (DSM-III or later) or the International Classification of Diseases (ICD-9 or 10) classification systems, and have satisfied these criteria on the basis of a structured clinical interview. Second, the researcher(s) must have been blind to the diagnosis (i.e., either schizophrenia or normal control) when reading the scans. This stipulation was made to ensure that the quality of the neuroimaging evaluation in each study was held relatively constant and did not influence the findings (see Damasio & Damasio, 1989). If the research article met the above criteria, its content variable(s) was included in our review. In the case of separately published studies that used the same participant samples, the decision rule was adopted to treat these studies as a single study with multiple independent variables (see Hedges & Olkin, 1985). The *d* statistic (Cohen, 1988) was calculated for each comparison as the difference between schizophrenia and control group means normalized by the pooled standard deviation. Effect sizes were derived whenever means and standard deviations were reported. Effect sizes were also calculated from inferential statistics based on formulas provided by Wolf (1986) when primary studies did not report central tendency and dispersion data. Effect sizes were not derived from *p* values.

Forty-eight studies published between 1980 and 1997 met criteria for inclusion in the present analysis. Sample size data of the study set are shown in Table 1. The table indicates how many studies were utilized in each of the meta-analyses, as well as the number of effect sizes that were

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Table 1. Sample size statistics for frontal-executive studies in schizophrenia

Index	*N*. studies	*N*. d	Schiz. *N*	Con. *N*
Structural imaging (MRI and CT)	22	33	761	658
Functional imaging (PET)	26	46	537	427
Total	48	79	1298	1085

N. studies = number of studies; *N*. d = number of effect sizes; Schiz. *N* = number of patients with schizophrenia; Con. *N* = number of control participants.

incorporated into each calculated mean effect size. The number of patients with schizophrenia and normal controls for each meta-analysis is also included. In total, neuroimaging results from 1,298 patients with schizophrenia, and 1,085 normal healthy controls were recorded across meta-analyses.

Recorded Variables

Recorded variables for each article used in our meta-analysis included the full study reference, any moderator variables reported (e.g., age, percent male, percent on medication, onset age, duration of illness, education, and the number of hospitalizations for patients with schizophrenia only; also the type of neuroimaging equipment along with the procedural outline—for example, T1/T2, length of cut, number of cuts, angle of cut (i.e., sagittal or coronal). These study characteristics were used to describe the study set retrieved and treated uniformly for moderator variable analysis.

For the structural imaging data, MRI and CT effect sizes were calculated for both bilateral frontal lobe volume and left frontal volume. Left frontal volumes were gathered in keeping with Suddath et al.'s (1990) finding of left hemisphere pathologic involvement in 14 of 15 monozygotic twin pairs discordant for schizophrenia. We defined the frontal lobes to refer to the rostral cerebral region superior to the Sylvian fissure and anterior to the Rolandic fissure (Benson & Miller, 1997; Damasio, 1991; Damasio & Anderson, 1993; Stuss, 1996; Stuss & Benson, 1986). Studies were included if the anatomic boundaries of the frontal lobe measurement fell within or were consistent with our definition. In practice, frontal lobe measurement varied with respect to the inclusion or exclusion of basilar–orbital, or primary motor and/or supplementary motor strip areas. In each case however, the dorsolateral prefrontal cortex was always included in the measurement of the lobe and thus, in the comparison to healthy normal controls. That is, in keeping with Brodmann's (1909, 1925) cytoarchitectonic divisions, areas 44, 45, and 47 that correspond roughly to the pars opercularis, pars triangularis, and pars orbitalis, respectively, areas 9 and 10 which constitute parallel bands occupying the frontopolar area in the superior and middle frontal gyri, area 46 which can be found on the anterior dorsolateral surface in the inferior portion of the middle frontal gyrus above the most lateral portion of area 10 and otherwise surrounded by area 9, and finally area 32 in the mesial surface of the frontal lobe which forms an anterior cap to the cingulate gyrus, were always included in defined measures of frontal lobe volume in primary studies. Our effects sizes are thus based on these cytoarchitectonic divisions of the frontal lobe. Effect size analysis and comparison of Brodmann areas 4, 6, 8, 11 and 24 was not possible due to an insufficient number of studies that reported detailed regional anatomical data.

Positron emission tomography findings that were gathered included cerebral blood flow studies that reflect the measurement of regional cerebral blood flow during continuous inhalation of $[^{15}C]O_2$. Frontal activity was calculated in primary studies from cerebral blood flow after additional measurements of the oxygen extraction fraction (i.e., the percentage of the available blood oxygen extracted during its passage through the brain vasculature usually measured after inhalation of $[^{15}C]O_2$). Also gathered were studies of regional blood volume, which is indexed by a correction for the percentage of any cerebral region that contains blood rather than brain (see Sawle, 1995). Finally, glucose metabolism studies were also gathered. These studies measured frontal activation after intravenous injection of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) which is metabolized by hexokinase to FDG-6-phosphate. For the varying PET procedures, at-rest and activated study conditions were recorded separately. Activation procedures utilized in primary studies included the WCST, the continuous performance test (Spreen & Strauss, 1998), somatosensory stimulation, smooth pursuit tracking, and motoric tracking of a geometric figure—all tasks with relative sensitivity to frontal-executive dysfunction. Anatomic boundaries had to fall within the rostral cerebral region superior to the Sylvian fissure and anterior to the Rolandic fissure with the inclusion of dorsolateral prefrontal cortex to be included in our review. Again, measures of frontal lobe function were confined to Brodmann areas 44, 45, 47, 9, 10, 46, and 32. Because of differences in test measures and indices, the PET findings are presented as a range as well as independently in order to parse out which PET procedures are most sensitive to indexing frontal brain system integrity in schizophrenia. It can further be argued that the varying PET procedures are qualitatively dissimilar and should therefore not be treated as common dependent variables (see Sawle, 1995).

Descriptive data available for demographic and clinical variables are presented in Table 2. The table reflects patient samples for both structural and functional studies that are typically male (78%) who were first diagnosed with schizophrenia at the age of 22. The modal patient was approximately 33 years of age, and had been admitted to hospital four times on average. Most patients have had 12 years of formal education. Finally the average patient was typically medicated and ill for 9 years. Note that the percent of patients with schizophrenia on medication presented in Table 2 is more informative than the CPZ equivalent daily dose because of infrequent neuroleptic dose reporting in the pub-

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Table 2. Descriptive statistics for structural and functional studies in schizophrenia

Imaging methodology variable	*Mdn*	*M*	*SD*	Range	*N*
Structural imaging (MRI and CT)					
Age	29.7	31.5	7.6	23.3/59.1	22
Onset age	21.0	21.3	1.5	19.7/23.9	5
Duration of illness (years)	6.8	7.7	4.5	1.6/16.8	12
Hospitalizations	5.0	5.2	1.4	3.8/7.1	5
Percent male	68.8	69.8	29.2	0.0/100.0	19
Percentage on medication	100.0	74.8	41.0	0.0/100.0	7
CPZ eq. daily dose in mg	337.5	337.5	477.3	0.0/675.0	2
Functional imaging (PET and rCBF)					
Age	29.6	30.5	4.8	23.2/39.2	26
Onset age	24.3	24.7	2.7	21.6/29.0	5
Duration of illness (years)	8.1	8.2	3.9	2.6/16.1	12
Hospitalizations	3.9	3.9	1.0	3.1/4.6	2
Percent male	81.8	81.0	17.8	33.0/100.0	24
Percentage on medication	41.0	42.6	44.5	0.0/100.0	23
CPZ eq. daily dose in mg	0.0	91.2	234.4	0.0/764.0	11

Mdn = median value; *M* = mean value; *SD* = standard deviation; *N* = number of times variable was reported.

lished literature. In addition, clozapine, and respiridone dosages are not convertible into CPZ doses. All antipsychotic medication, however, is reflected in the binary medication variable. None of the sample patient descriptive or demographic variables differed significantly between structural and functional studies.

To address the issue of improved imaging spatial resolution over time and its possible effect on the magnitude of the effect size, we computed an unweighted multiple regression with date of publication as a covariant, which proved to be insignificant. We also analyzed, however, the different imaging techniques separately, rather than *en masse*, using Pearson product-moment correlations. We found a significant relation between PET effects and date of publication ($r = .40$ $p < .05$), but no such relation for the CT and MRI effects.

RESULTS

Structural Imaging

Mean effect size values for frontal brain volume and left frontal brain volume from CT and MRI studies are included in Table 3. There were 10 CT and 12 MRI studies with corresponding mean effect sizes of -0.62 (OL% = 62) and -0.14 (OL% = 90) respectively. A two-tailed independent sample *t* test on CT *versus* MRI effects revealed a significant difference [$t(21) = -3.50$, $p < .005$] indicating that more accurate neuroanatomic measures (i.e., MRI) associate with smaller effect sizes. Moreover, statistical comparison of left frontal and bilateral frontal effects did not reach significance, indicating no support for the idea that the left frontal region is preferentially affected in schizophrenia. The effect sizes correspond to 75% (left frontal) and 90% (bilateral) overlap between patients and healthy controls according to Cohen's (1988) idealized population distributions. That is, using CT/MRI left frontal measurement as an example, approximately 75% of patients with schizophrenia display left frontal structures that are indistinguishable from normal control values.

In terms of possible moderator variables, there were no significant product-moment correlations between basic scanning (e.g., T1 or T2, type of scanner, length of cut) and clinical variables (medicated *vs.* nonmedicated, age, onset age, duration of illness, percent male) and the structural imaging effect sizes. Moreover, a two-tailed independent sample *t* test of effects from MRI T1 *versus* T2 tissue imaging characteristics did not reach a statistically significant difference. Further, a comparison of sagittal *versus* coronal cuts using a similar statistical comparison did not reveal a significant difference in obtained effects.

Functional Imaging

The mean effect sizes from 26 PET studies are shown in Table 3 for resting and activated conditions. These studies

Table 3. Summary of evidence of frontal brain system deficits in schizophrenia

Index	*Md*	*SD*	*N*	95% C.I.
Frontal brain volume	−0.36	0.46	22	−0.55/−0.17
Left frontal brain volume	−0.16	0.18	11	−0.27/−0.05
Positron emission at rest	−0.64	0.62	21	−0.91/−0.38
Positron emission activated	−1.13	0.61	9	−1.53/−0.73
Left frontal positron emission	−0.50	0.61	16	−0.80/−0.21

Md = mean effect size; *SD* = standard deviation of effect size; *N* = number of studies; 95% C.I. = 95% confidence interval in which bounds of estimate within which effect size will fall 95% of the time.

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Table 4. Frontal brain functional imaging activation studies of schizophrenia

Study	Activation task	*d*	Overlap
Volkow et al. (1986)	Tracking a geometric figure	−2.09	17%
Berman et al. (1986)	Wisconsin Card Sorting Test	−1.68	25%
Weinberger et al. (1986)	Wisconsin Card Sorting Test	−1.78	23%
Weinberger et al. (1988)	Wisconsin Card Sorting Test	−0.89	49%
Cohen et al. (1987)	Continuous Performance Test	−0.28	80%
Buchsbaum et al. (1990)	Continuous Performance Test	−0.57	63%
Buchsbaum et al. (1992)	Continuous Performance Test	−1.27	36%
Volkow et al. (1987)	Smooth pursuit tracking	−0.93	47%
Ebert et al. (1993)	Somatosensory stimulation	−0.69	58%

Note. Studies by Berman et al. (1986), Weinberger et al. (1986, 1988) and Ebert et al. (1993) measured cerebral blood flow and the remaining studies measured glucose metabolism. Studies by Weinberger et al. (1986, 1988) and Buchsbaum (1990) studied unmedicated patients and the remaining studies studied medicated patients.

included both glucose metabolism and blood flow methods. Note that no significant differences were found between methods in terms of average effect sizes and the studies were therefore compiled into a single functional imaging data set. The mean effect size from resting state PET studies is −0.64, indicating that schizophrenia patients as a group have lower frontal physiological activity than healthy controls. This effect also corresponds to approximately 60% overlap in patient–normal control distributions. When activation tasks such as the WCST or the Continuous Performance Test were used during the scanning procedure the mean effect size was −1.13, which corresponds to approximately 40% schizophrenia–control group distribution overlap.

As can be seen from the tables, there is almost a twofold increase in the magnitude of effect when participants undergoing metabolism or blood flow scans engage in cognitive activity instead of maintaining a resting condition. It is also apparent, however, in view of the standard deviation and confidence intervals, that heterogeneity of effects is present. Positron emission and blood flow studies using activation tasks yielded effects that ranged from −0.57 to −2.09. Further, the same activation tasks seem to produce highly variable effects in different studies (e.g., WCST, −.89/−1.78; Continuous Performance Test, −.28/−1.27). Moreover, given the large obtained effect on PET during the tracking of a geometric figure (*M* effect = 2.09), there is little evidence to suggest that the WCST is an optimal activation task (*M* effect across studies = 1.45) in comparison to tracking figures, Continuous Performance (*M* effect across studies = 0.71), smooth pursuit tracking (*M* effect = 0.93), or somatosensory stimulation (*M* effect = 0.69).

Moderator variable analysis of the functional imaging results revealed two significant product-moment correlations. First, a significant relationship was found between duration of illness and the functional imaging effects [$r(12) = -0.73$, $p < .01$, two-tailed]. Second, a significant relationship was found between the percentage of male participants in patient study samples and the neuroimaging effects [$r(24) = -0.42$, $p < .05$, two-tailed]. Therefore, patient–control differences in frontal metabolism and blood flow diminish as a function of illness chronicity and proportion of male patients in the study sample. In other words, hypofrontal physiological deficits are maximal in more acutely ill patient samples that also have more balanced gender composition. Frontal physiological function in schizophrenia approximates normal values increasingly when more chronic samples with a high proportion of male participants constitute the basis for comparison with controls.

Reduced frontal activity and disease progression has not been found to be a function of long-term use of neuroleptic pharmacotherapy (see Berman et al., 1986; also see Spohn & Strauss, 1989). Although we were able to extract CPZ equivalent daily dosages and percentage on medication variables, the available literature did not include a "years on medication" variable that would allow us to test directly this finding. Moreover, in keeping with the significant correlation between hypofrontal activity and the percentage of males, future research is needed to compare male and female participants on PET measures of hypofrontal activity. The present data imply more severe hypofrontal deficit in men than women with schizophrenia, and this does not seem to be a function of increased neuroleptic dosages and duration of usage in men with the illness (also see Goldman et al., 1996).

DISCUSSION

The results of this quantitative review suggest that researchers may have overestimated the importance of the frontal brain region in the pathophysiology and behavior of schizophrenia. The neuroimaging literature provides reliable evidence of frontal deficit in schizophrenia–control comparisons. The average magnitude of difference between schizophrenia and healthy controls, however, is generally too weak to support the idea that frontal brain dysfunction is a necessary component of a unitary schizophrenic illness. This weakness is most apparent in average effects obtained for frontal brain volume (*M* = −.36), left frontal brain vol-

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ume ($M = -.16$), frontal resting metabolism and blood flow ($M = -.64$). Effect sizes of this magnitude imply that schizophrenia and control distributions overlap by as much as 88% and no less than about 60% on structural and functional measures of the frontal lobes. Moreover, there is evidence that newer and more accurate technology in the form of magnetic resonance neuroimaging yields smaller effect sizes than an earlier literature based on CT scanning. It is only when behavioral measures are employed as activation tasks during frontal blood flow and metabolism studies, that average effect sizes rise in magnitude to indicate patient–control distribution overlaps that are less than 50 percent. The magnitude of effects based on PET, however, is related in part to illness duration and to gender composition of patient samples. The largest frontal physiological effects seem to occur in acutely ill female schizophrenia patients.

The finding that neuroimaging paradigms that incorporate behavioral requirements are more sensitive than resting scans to schizophrenic illness is consistent with the literature on neurocognitive deficits in schizophrenia (see Heinrichs & Zakzanis, 1998). Behavioral measures of putative executive functions like card sorting and phonemic word generation are consistently more sensitive than standard structural or functional neuroimaging measures to the presence of schizophrenia (e.g., Raz & Raz, 1990). At the same time, it is important to note that the neuroanatomic specificity of the most widely used behavioral measures is questionable. Both the WCST and word fluency measures are influenced by disturbances in nonfrontal regions (Anderson et al., 1991; Corcoran & Upton, 1993; Heaton et al., 1993; Heinrichs, 1990; Stuss et al., 1998). Moreover, WCST effect sizes may be tied to general intellectual ability in this population (Heinrichs & Zakzanis, 1998). This neuroanatomical nonspecificity of "frontal" tasks and the effectiveness of general attentional and perceptual tasks in activating frontal cortex, makes it difficult to use the behavioral findings to support the idea of a selective frontal brain contribution to the illness.

It appears that the neuropsychological profile of patients with schizophrenia is consistent with a diffuse dysfunction that may or may not include the frontal cortex. The evidence suggests that the illness involves a very broadly based cognitive impairment with maximal deficit in aspects of verbal memory, language, and possibly, in interhemispheric transfer skill (Cullum et al., 1990; Heinrichs & Zakzanis, 1998; Palmer et al., 1997; Randolph et al., 1993; Saykin et al., 1991, 1994). This broad impairment implicates numerous neuroanatomic structures and echoes recent speculations about the pathophysiology of schizophrenia that emphasize multiple neural sites, systems and putative circuits (Adler et al., 1998; Andreasen et al., 1998; Gray, 1998).

In light of these considerations, there are basically three ways of understanding the very moderate prevalence of frontal-executive deficit in schizophrenia. First, it is possible to hold that such deficit is secondary, peripheral, rather than central to the illness. That is, most diseases have peripheral features that are tied only modestly and indirectly to the primary pathology. For example, overall brain volume reductions are less prevalent in early stage Alzheimer's disease than volume reductions of a specific structure, the hippocampus (Seab et al., 1988; Zakzanis, 1998b). Presumably, this reflects the primary locus of pathology in the hippocampus and other specific structures and the less direct relation of this focal pathology to general changes in brain volume. Accordingly, focal frontal system dysfunction may be slightly elevated in schizophrenic illness, but as a weak byproduct, with no causal link to the essential and still undiscovered pathology.

A second way of understanding the magnitude of frontal effects in schizophrenia is to say that frontal disturbance is an important but transitory feature of the illness. Theories like the recent neural diathesis–stress models described by Walker and Diforio (1997) and Weinberger (1987) argue that frontal dysfunction is maximal in early phases of the illness as age-linked surges in stress hormones potentiate dopamine activity in the limbic system and overwhelm frontal regulation to cause positive symptoms. Frontal involvement, however, is not obligatory in Walker and Diforio's view. Hormonal and dopamine-related regulatory failures may also occur in the hippocampus or may be due to perinatal insults that are "unmasked" by maturing brain systems. This kind of analysis is congruent with our findings of modest and variable frontal effects and of a relation between reduced frontal activity and duration of illness. Thus, transitory frontal dysfunction may be one aspect of one pathway that can lead to schizophrenia.

Finally, it is clear that the average magnitude of difference between patients with schizophrenia and healthy controls on neurobiological measures is generally too modest to support the idea that frontal brain dysfunction is a necessary component of a unitary illness model of schizophrenia. Hence, a third way of understanding our findings is to argue that a frontal variant of schizophrenia exists in some unknown proportion within a heterogeneous patient population. It follows that there may be many subtypes of schizophrenia and that each subtype reflects a different cluster of neurobiologic alterations (see Carpenter et al., 1993; Heinrichs, 1993; Liddle & Barnes, 1990). That is, schizophrenia, as currently defined, may be an umbrella term for several different diseases, only one of which has pronounced involvement of the frontal brain region (see Heinrichs, in press). Other variants may focus primarily on temporal–hippocampal dysfunction, while still other variants may appear neuropsychologically normal, perhaps reflecting phasic neurotransmitter changes that are not captured by standard cognitive tests (see Heaton & Palmer, 1998; Heinrichs & Awad, 1993; Heinrichs et al., 1997; Palmer et al., 1997). In researching such a typology, it will be important to identify the subtypes clearly and to ensure sample sizes that are large enough to detect their existence.

In conclusion, we addressed the strength and consistency of published research on the frontal-executive system in patients with schizophrenia in our quantitative review. This literature has accumulated in support of the hypothesis that

schizophrenia is a neurological disorder with a core deficit in the frontal lobes that manifests itself in disturbed executive-type behavior. Our quantitative syntheses (also see Heinrichs & Zakzanis, 1998) shows that the published evidence on the integrity of frontal structure and physiology is modest and variable. It is hard to justify the persistent emphasis placed on the importance of the frontal lobes in schizophrenia in view of our findings. The modest evidence for frontal deficit in the illness may mean that the frontal system is peripheral to the basic pathophysiology, or essential but transitory in contributing to the illness, or essential, but only for a proportion of patients that have a frontal-type variant of schizophrenia. As the resolving power of neuroimaging improves and the importance of detailed cellular analysis derived from *postmortem* tissue is recognized (e.g., Akbarian et al., 1993), it may be possible to decide between these hypothetical roles for the frontal brain in the neurogenesis of schizophrenia.

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