Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies

Objective: Hypofrontality is not a well-replicated finding in schizophrenia either at rest or under conditions of task activation.
Method: Studies comparing whole brain and frontal blood flow/metabolism in schizophrenic patients and normal controls were pooled. Voxel-based studies were also combined to examine the pattern of prefrontal activation in schizophrenia.
Results: Whole brain flow/metabolism was reduced in schizophrenia to only a small extent. Resting and activation frontal flow/metabolism were both reduced with a medium effect size. Duration of illness significantly moderated resting hypofrontality, but the moderating effects of neuroleptic treatment were consistent with an influence on global flow/metabolism only. Pooling of voxel-based studies did not suggest an abnormal pattern of activation in schizophrenia.
Conclusion: Meta-analysis supports resting hypofrontality in schizophrenia. Task-activated hypofrontality is also supported, but there is little from voxel-based studies to suggest that this is associated with an altered pattern of regional functional architecture.

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Introduction

As it has become clear that structural brain pathology in schizophrenia is modest, and with neurochemical and other investigations remaining inconclusive (1, 2), functional imaging has become the most promising candidate for identifying dysfunctional brain systems in the disorder. The major finding to emerge from these studies has been hypofrontality, a loss of the normal pattern of higher resting cerebral blood flow or metabolism in anterior than posterior regions. Hypofrontality has become one of the most widely cited and influential findings in the literature on schizophrenia, which is referred to in the introduction or discussion of many biological research papers and which has led most if not all contemporary theoretical approaches to invoke some form of executive dysfunction (3–7).

Hypofrontality was first documented in 1974 by Ingvar and Franzen (8) who used the ^{133}Xenon technique to compare groups of schizophrenic patients with short and long durations of illness to a control group of abstinent alcoholics. The finding was replicated in a number of subsequent studies, some of which used the newly developed technique of photon emission tomography (PET) (9–12). From the outset, however, there were negative reports (13–16), and conflicting findings have continued to dog the field to the present day (e.g. 17). In a recent review, Chua and McKenna (18) found that hypofrontality was present in only a third of studies selected on the basis of simple methodological considerations, and in an editorial entitled 'Hypofrontality in schizophrenia: RIP'. Gur and Gur (19) argued that the finding was a shibboleth, which had only meagre experimental support.

Partly in response to these inconsistencies, Weinberger et al. (20) proposed that hypofrontality in schizophrenia might be more easy to demonstrate when cognitive demands were made on the prefrontal cortex. They found that a group of chronic schizophrenic patients showed only a trend

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towards hypofrontality at rest, but markedly failed to activate the prefrontal cortex when they performed a prototypical executive task, the Wisconsin Card Sorting Test. Like resting hypofrontality, however, task-related or activation hypofrontality has not been consistently replicated. This applies not only to studies using executive tasks (18, 21), but also to those using memory and vigilance tasks (17, 18), which also activate the prefrontal cortex (22).

The most recent development in the functional imaging of schizophrenia has been the use of voxel-based image analysis techniques such as statistical parametric mapping (SPM). Instead of measuring the average activity across an anatomically defined 'region of interest', these studies make voxel-by-voxel comparisons across the entire brain, and identify clusters of significant activation in response to a cognitive task. Voxel-based techniques have now largely replaced studies using the region of interest approach. However, they have brought their own problems, methodological, statistical (particularly how to correct for the large number of comparisons), and even philosophical. For example, a current area of controversy concerns whether task-related hypofrontality in schizophrenia reflects an intrinsic functional brain abnormality or whether it merely indexes schizophrenic patients' poor performance on frontal tasks (21, 23).

Aims of the study

As a finding which is not well supported by 'vote counting' of positive and negative findings, hypofrontality in schizophrenia is a suitable candidate for meta-analysis. This systematic review addresses the questions of whether whole brain flow/metabolism is reduced in the disorder, whether there is resting hypofrontality, and whether hypofrontality appears under conditions of neuropsychological task activation. Not included in these analyses are a considerable number of activation studies which have used voxel-based techniques, which cannot be meta-analysed in the conventional way because it is not possible to derive effect sizes from them. These, however, can be combined using a novel technique which allows the *pattern* as opposed to the *degree* of prefrontal activation to be examined in schizophrenia.

Material and methods

Papers reporting functional imaging studies on schizophrenic patients were searched electronically from January 1974, the year of publication of

Ingvar and Franzen's study (8) to July 2003. Studies were identified through MEDLINE, PSYCHINFO and EMBASE using the key words 'schizophrenia', 'tomography, emission-computed', 'magnetic resonance imaging', 'brain mapping', 'cerebral cortex', 'frontal lobe'. The electronic search was supplemented by checking of review articles on functional imaging in schizophrenia and the reference lists of all research papers obtained. Hand searching of key journals was also carried out from 1981, the year of the first replication of Ingvar and Franzen's (8) study. The journals searched were *Acta Psychiatrica Scandinavica*, *American Journal of Psychiatry*, *Archives of General Psychiatry*, *British Journal of Psychiatry*, *Biological Psychiatry*, *Psychiatry Research*, *Schizophrenia Research* and the *Journal of Cerebral Blood Flow and Metabolism*.

When studies reported on overlapping groups of patients or controls, the study with the largest number of schizophrenic patients that provided usable data was used. Studies published as brief reports or letters were included, but findings in abstracts from conference proceedings were not. The small number of non-English-language papers located in the search (approximately five) were found not to contain usable data.

To be included, studies had to use diagnostic criteria for schizophrenia, schizoaffective or schizophreniform disorder and compare adult patients with normal controls. Studies reporting findings on adolescents or only on patients aged over 65 were excluded. Age and sex matching were not required as inclusion criteria, as virtually all studies matched patients and controls on these variables. Almost all the studies also used prospectively ascertained volunteer controls.

Data obtained from each study were converted into an effect size d, the difference between the mean for the patient and control groups divided by their pooled standard deviation. Hedges' correction was used (24); this corrects for the tendency of small studies to overestimate the population effect size. Where mean and standard deviations were not available t-values, F-values or P-values were used. In several cases data were extracted from graphs or scatter plots using a digitizing program ('Ungraph', http://www.biosoft.com). Authors were contacted if effect sizes could not be extracted from any of the published data. All effect sizes were extracted a second time independently and differences resolved.

Individual effect sizes were combined to produce an overall effect size, with each d-value weighted by the reciprocal of its variance. Analysis of moderator variables was based on the weighted effect size

for each study. The Q statistic was used for categorical variables (24) and Rosenthal's focused comparison for continuous variables (25). As well as technique (see below), variables included age, treatment, duration of illness and year of publication. Analyses were carried out by means of DSTAT 1.10 (26) which uses a fixed effects model.

Meta-analysis of functional imaging studies presents a number of challenges. Perhaps the most important of these is that three main techniques have been used, ^{133}Xenon inhalation, single photon emission tomography (SPECT) and PET. One way to proceed would be to carry out separate meta-analyses for each of these techniques. However, the methodological differences within each technique – for example, the use of measures of cerebral blood flow ($^{15}O_2$) or metabolism (fluorodeoxyglucose, FDG) in PET studies, and the use of different radiotracers in SPECT, would make any decisions about how to divide the studies difficult and ultimately arbitrary. Furthermore, meta-analysis is explicitly designed for the purpose of combining heterogeneous sets of data. We, therefore, chose first to meta-analyse all types of study together and then to examine technique as a moderator variable.

Other methodological issues relate specifically to the meta-analyses of (a) whole brain blood flow/metabolism, (b) resting hypofrontality, and (c) activation hypofrontality.

Whole brain blood flow/metabolism

SPECT, as normally employed, is a relative technique – measures of blood flow are made relative to some reference region which is typically the whole brain or hemisphere. Although it cannot therefore be used to provide a measure of whole brain blood flow, a small number of studies were found which did report findings for whole brain flow. For example, these used the cerebellum as a reference region, or employed a mathematical model to derive absolute flow rates. The whole brain studies were therefore meta-analysed first excluding these studies and then including them.

Resting hypofrontality

Meta-analysis of these studies is complicated by the use of both absolute and relative measures of frontal blood flow/metabolism. Studies using the former compare raw values for the frontal region between patients and controls, whereas the latter divide frontal values by those for a reference region such as whole brain or hemisphere. A preliminary analysis of 14 studies which reported

both absolute and relative values revealed that the same study quite frequently produced widely different effect sizes for hypofrontality, and so the two sets of data were meta-analysed separately.

Activation hypofrontality

One difficulty in combining these studies is the wide variety of neuropsychological tasks used. For the purposes of this meta-analysis, only studies employing tasks known to activate the prefrontal cortex in normal subjects were included. Decisions were based on the reviews of Cabeza and Nyberg (22) and Fletcher and Henson (27), and the tasks included were executive, working memory, long term memory and vigilance.

Voxel-based studies

As noted in the introduction, studies of activation hypofrontality fall into two classes, those using region of interest techniques, and those using voxel-based methodologies. While voxel-based studies commonly report findings on the *degree* of activation in schizophrenic patients compared with controls, the data they generate cannot be used to generate effect sizes, and to the authors' knowledge no other technique has been developed for combining such findings across studies. What can be meta-analysed is differences in the *pattern* of activation found across these studies. Thus, Duncan and Owen (28) plotted peak activation foci activation in normal subjects from 20 studies using a range of different tasks onto a rendered brain. They then examined the homogeneity of activated regions between tasks using a three-dimensional version of the Kolmogorov–Smirnov test (KS3) developed by one of us (29). Like the original Kolmogorov–Smirnov test this examines whether two distributions – in this case two three-dimensional spatial distributions of peak activation foci – differ significantly. The test is non-parametric and does not require assumptions of independence of observations, and so is not affected by the fact that each of the combined studies gives rise to more than one focus of activation. The algorithm for KS3 can be described in spatial terms as follows:

[A] A base point is chosen in xyz space and planes parallel to $x = 0$, $y = 0$ and $z = 0$ are drawn through it dividing the space into eight cells (octants).
[B] The percentage of each type of point on the eight octants is calculated.

[C] The absolute value of the differences between the two percentages is calculated for each octant and the largest difference is noted.

[D] The base point is moved so that the difference at [C] is maximized.

This maximized difference is KS3 and represents the biggest discrepancy between the two samples that can be achieved by such orthogonal cellular partitions.

The significance of the observed KS3 statistic is assessed using a bootstrap Monte Carlo resampling method (30).

Results

The search yielded approximately 180 papers reporting data on schizophrenic patients. Of these, only 103 provided usable data. This was primarily because of overlap between the studies reported, but also to a lesser degree because of lack of controls in a number of studies (or use of inappropriate controls, such as patients with depression).

Whole brain blood flow/metabolism

Studies were included which reported whole brain or hemisphere data. Studies which reported on an inclusive set of brain regions (e.g. frontal, temporal, parietal, occipital) were not combined. Studies were included where scanning was carried out under resting conditions. Studies where imaging was carried out during performance of neuropsychological tasks, frontal or otherwise were excluded. However, a small number of studies which examined subjects during sensory stimulation procedures such as mild electric shock to the forearm were included.

Twenty-nine studies (9, 12, 16, 17, 31–54) provided global or hemisphere data (in which case left and right values were averaged). The pooled effect size for these was −0.27 (CI −0.39 to −0.15) with the negative sign indicating reduced flow/metabolism in schizophrenia (see Table 1). These studies consisted of 17 using ^{133}Xenon and 11 using PET (plus one using a non-radioactive technique, Xenon CT).

Four further studies (55–58) reported whole brain findings using the relative technique of SPECT (see above). Inclusion of these studies changed the pooled effect size only slightly to −0.28 (CI −0.39 to −0.17).

The original 29 studies were not homogeneous [$Q(27) = 72.46$, $P < 0.0001$], but homogeneity was achieved by exclusion of seven outliers (9, 31, 34, 40, 42, 45, 47) This reduced the effect size to −0.26 (CI −0.40 to −0.11; $Q = 29.60$, $P = 0.10$). Four of the seven outliers had large negative values, but otherwise they showed no common features.

A funnel plot of the original 29 studies is shown in Fig. 1. This indicates skewing towards studies with negative effect sizes and an absence of small studies with a positive effect size. This in turn suggests publication bias against studies failing to find decreased whole brain blood flow/metabolism in schizophrenia.

Findings for the moderator variables are summarized in Table 1. Treatment was highly significant. The effect size for 14 studies using untreated

Table 1. Pooled effect sizes and significant moderator variables for cerebral blood flow/metabolism in schizophrenia

	No. of studies	Total N	Effect size (d)	Confidence interval	Moderators of effect size
Whole brain	22	795	−0.26	−0.40 to −0.11	Age (trend) Duration Neuroleptic treatment Year of publication (trend)
Resting hypofrontality (relative)	38	1474	−0.32	−0.43 to −0.21	Age Duration (trend) Acute vs. mixed vs. chronic Year of publication
Resting hypofrontality (absolute)	25	950	−0.55	−0.68 to −0.41	Age Duration Acute vs. mixed vs. chronic Neuroleptic treatment Year of publication
Activation hypofrontality (relative)	17	685	−0.37	−0.53 to −0.22	Technique Task performance (trend)
Activation hypofrontality (absolute)	10	347	−0.42	−0.65 to −0.20	−

No. of studies, total N and effect sizes are for the homogeneous subsets of the studies in each analysis.
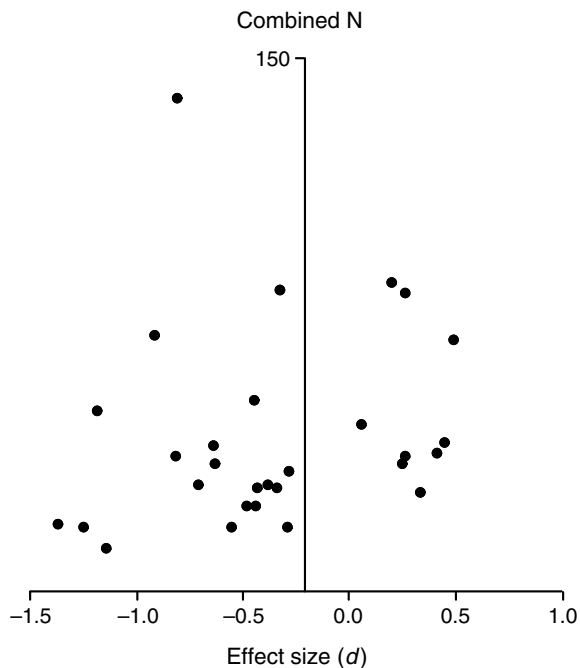
Fig. 1. Funnel plot of 29 studies of whole brain blood flow/metabolism in schizophrenia.

patients was −0.08 compared with −0.63 in eight studies using treated or mostly treated patients [QB(1) = 14.90, P = 0.0001]. Technique did not moderate effect size [ES for 17 Xenon and 11 PET studies: −0.21 vs. −0.29, QB(1) = 0.33, P = 0.56]. Age showed a trend towards being a significant moderator (Z = −1.81, P = 0.07) with greater reduction in whole brain flow/metabolism in schizophrenia with increasing age.

The moderating effect of chronicity was examined in two ways. Data on mean duration of illness was recorded in 21 studies and was significant when modelled as a continuous variable (Z = −2.42, P = 0.01); compared with controls, schizophrenic patients showed progressively lower brain flow/metabolism with increasing duration of illness. Additionally, the patient samples were classified as acute (first episode patients or maximum duration of less than 2 years) chronic (duration 2 or more years) and mixed; this could be achieved in 26 studies [yielding 28 values – two studies (39, 50) included separate groups of acute and chronic patients compared with the same control group]. This yielded progressively larger effect sizes with increasing chronicity (ES = −0.09 for five acute studies; −0.18 for eight studies on mixed patients; −0.35 for 15 chronic studies); however, the difference was not significant [QB(2) = 2.88, P = 0.24].

Year of publication moderated effect size at trend level (z = −1.81, P = 0.07).

Resting hypofrontality

Studies were included which reported comparisons for the prefrontal cortex, or the entire frontal cortex, or subregions thereof such as the dorsolateral prefrontal cortex. Where studies reported separate findings for different subregions, these were averaged, as were findings for left and right hemispheres. As with the whole brain analysis, studies were included which were carried out during procedures such as mild electrical shock (and one where subjects dealt cards into piles), but not where imaging was during performance of any kind of neuropsychological task.

Forty-seven studies reported values for relative frontal blood flow/metabolism (10–12, 14, 32, 33, 35, 40–43, 47, 50–55, 57, 58–86). The pooled effect size for these was −0.24 (CI −0.34 to −0.15). These studies were heterogeneous (Q = 135.00, P < 0.0001), but homogeneity was achieved by excluding nine studies (33, 40, 43, 51, 59, 60, 65, 69, 79, 82); this increased the pooled effect size −0.32 (CI −0.43 to −0.21; Q = 51.70, P = 0.10). The outliers included [133]Xenon, SPECT and PET studies and had no other obvious features in common.

Twenty-nine studies reported absolute frontal values (9, 11, 12, 13, 17, 31, 33, 35–37, 39–41, 45, 49–51, 53, 54, 56, 62, 63, 74, 80, 82, 83, 87–90) and these gave a pooled effect size of −0.33 (CI −0.44 to −0.21). These studies were also heterogeneous (Q = 63.77, P = 0.0001) but homogeneity was achieved by excluding four studies (11, 17, 40, 74). The increased the pooled effect size to −0.55 (CI −0.68 to −0.41; Q = 32.73, P = 0.11).

Funnel plots of the 47 relative and 29 absolute studies are shown in Fig. 2. In both cases these appear reasonably symmetrical and do not suggest publication bias against studies failing to find hypofrontality.

Analysis of moderator variables produced broadly similar results in the relative and absolute datasets. Therefore, except where there were differences, only the results for the relative studies are reported (the findings for both sets of studies are summarized in Table 1). As in the whole brain analysis, technique did not significantly moderate effect size. The pooled effect size for 10 studies using [133]Xenon was −0.31; that for 19 studies using SPECT was −0.11; and that for 18 studies using PET was −0.33 [QB(2) = 4.19, P = 0.12]. Although not significant, SPECT studies as a group tended to produce less hypofrontality than the other two techniques (see Fig. 3).

Medication was not a significant moderator of effect size in the relative studies [ES for 13 studies on untreated patients: −0.15; ES for 24 studies of
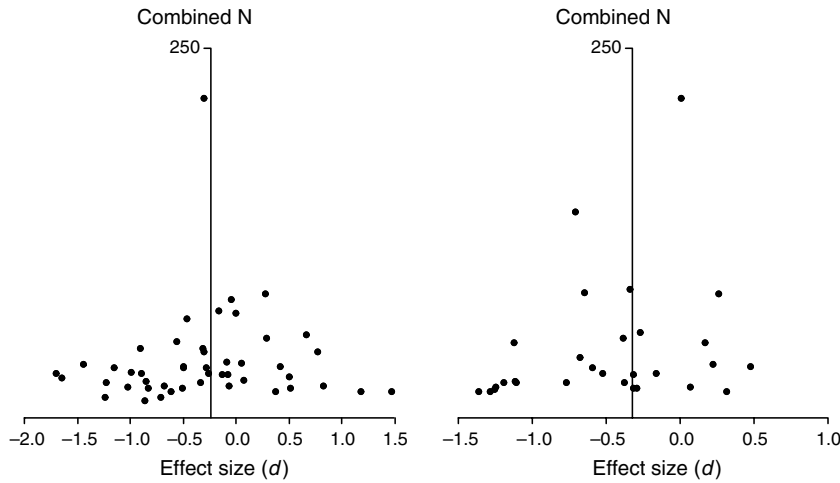
Fig. 2. Funnel plots of 47 studies of relative hypofrontality and 29 studies of absolute hypofrontality in schizophrenia.
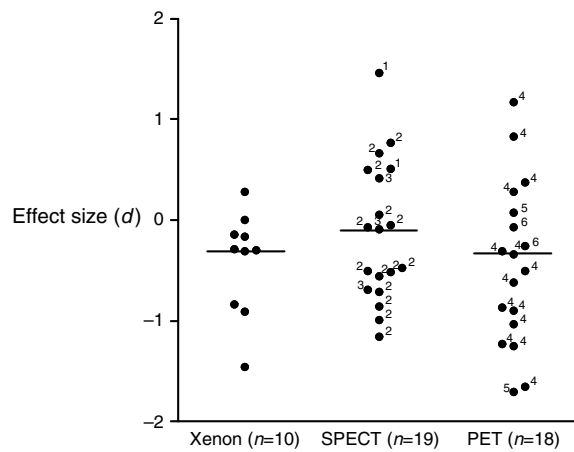

Fig. 3. Scatter plots of effect sizes for hypofrontality in schizophrenia, by technique. Lines indicate pooled effect size. Xenon studies include those designated as Xenon-SPECT. 1, HMPAO SPECT; 2, Tc SPECT; 3, Imp SPECT; 4, FDG PET; 5, ^{11}C PET; 6, ^{15}O$_2$ PET.
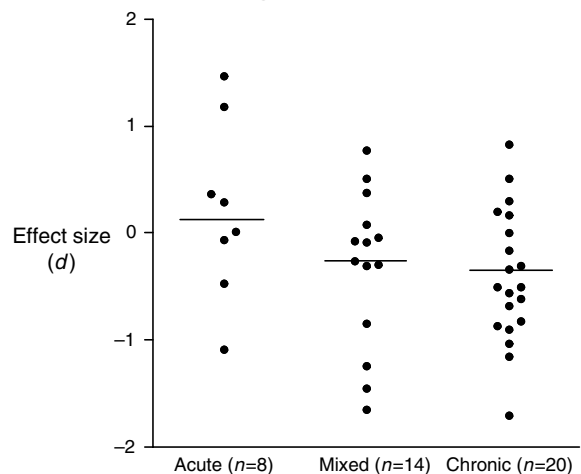
Fig. 4. Scatter plots of effect sizes for relative hypofrontality in studies carried out on acute, mixed and chronic schizophrenic patients. Lines indicate pooled effect sizes.

treated patients: −0.32, QB(1) = 1.62, P = 0.20]. However, it did moderate effect size in the absolute studies [ES for 14 studies of untreated patients: −0.15; ES for 10 studies of treated patients = −0.61, QB(1) = 9.92, P = 0.002].

Age was a significant predictor of effect size (Z = −2.53, P = 0.01), with greater hypofrontality being found with increasing age. Duration of illness, recorded in 33 of the 47 relative studies, bordered on significance as a predictor of effect size (Z = −1.93, P = 0.05), with increasing chronicity being associated with greater hypofrontality. In order to examine this further, patient samples were classified as acute, mixed and chronic (as described above) in 42 relative studies [including three (40, 50, 61) reporting separate groups of acute and chronic patients]. This revealed a significant difference: the effect size

for eight acute studies was +0.12; that for 14 mixed studies was −0.25; and that for 20 chronic studies was −0.34 [QB(2) = 9.66, P = 0.008] (see Fig. 4).

Year of publication was significant as a moderator variable (Z = 2.50, P = 0.01). More recent studies tended to find less hypofrontality.

Activation hypofrontality

Region of interest studies. As with resting hypofrontality, separate meta-analyses were carried out for studies reporting relative and absolute data. The pooled effect sizes were −0.45 (CI −0.60 to −0.30) for 18 relative studies (20, 58, 62, 64, 65, 70, 71, 76, 78, 91–100) and −0.42 (CI −0.65 to −0.20) for 10 absolute studies (17, 20, 39, 56, 62, 99, 101–104). The relative data were heterogeneous (Q = 35.07, P = 0.006), but only one study had to be removed

to achieve homogeneity [the combined studies of Weinberger et al. (20, 100) which used the same control group]. This reduced the effect size to −0.37 (CI −0.53 to −0.22, $Q = 23.08$, $P = 0.11$). The absolute data were homogeneous ($Q = 15.64$, $P = 0.07$).

Of the above moderators of effect size, the only one found to be significant was technique. In the relative studies the pooled effect size was significantly greater for the four [133]Xenon studies than for the eight SPECT and six PET studies [−0.91 vs. −0.38, and −0.33, QB(2) = 7.40, $P = 0.02$]. However, this difference disappeared when the [133]Xenon study of Weinberger et al. (20, 100), which had a large outlying effect size of −1.43, was excluded [QB(2) = 0.61, $P = 0.74$]. In the absolute studies the pooled effect sizes for six [133]Xenon studies and three PET studies did not differ [−0.37 vs. −0.35, QB(1) = 0.01, $P = 0.94$].

Two new moderator variables were also examined, *type of neurological task* and *task impairment*. Type of neurological task did not significantly influence effect size in the relative studies [ES for 10 studies using executive tasks, four using vigilance tasks and four using memory tasks: −0.54, −0.41, −0.21, respectively, QB(2) = 2.44, $P = 0.29$]. Task impairment, as indexed using the effect size of the difference between patients and controls in cognitive test performance, revealed a trend to significance in the 14 studies which reported these data ($Z = 1.86$, $P = 0.06$); poorer performance was associated with greater hypofrontality. These findings are shown in Fig. 5.

Activation hypofrontality, as measured by a simple comparison between patients and controls,
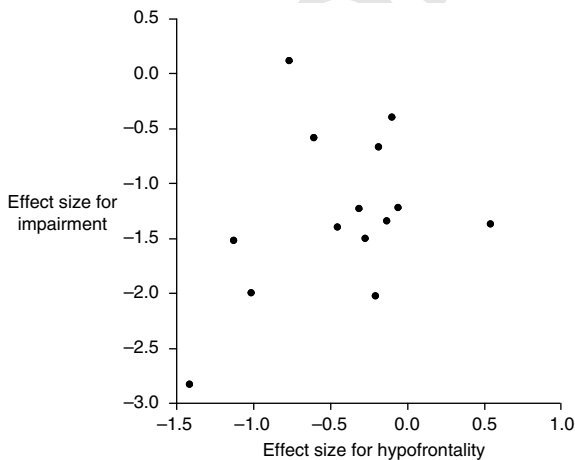
is potentially confounded by resting hypofrontality – it is possible that schizophrenic patients could increase their prefrontal blood flow/metabolism to the same degree as controls, but still show comparatively lower activation by virtue of their lower resting level. Therefore, effect sizes were calculated for activation *within* each group, i.e. the magnitude of the change from rest to activation in schizophrenic patients and in normal controls. Because only 14 studies reported both resting and activation data (17, 20, 39, 56, 58, 62, 64, 65, 70, 71, 76, 96, 99, 103) the absolute and relative studies were combined for this analysis. Schizophrenic patients increased their blood flow/ metabolism insignificantly from rest: the pooled effect size was +0.14 (CI = −0.05 to +0.33), which fell to +0.03 (CI −0.16 to +0.23) in a homogeneous set of 12 studies [$Q(12) = 20.12$, $P = 0.06$]. In contrast, the corresponding increase for controls was greater and significant +0.24 (CI = +0.03 to +0.46) These data were homogeneous ($Q = 17.23$, $P = 0.19$). Direct comparison of the individual effect sizes in patients and controls using Rosenthal's (27) focused comparison was significant at trend level ($Z = 1.87$, $P = 0.06$).

Voxel-based studies. Studies were included if they provided peak activation coordinates for schizophrenics and controls separately and used executive, memory and vigilance or working memory tasks. Following Duncan and Owen (28), differences in reference brains and significance thresholds across studies were ignored.

Fourteen studies (105–118) were found (seven PET and seven fMRI). A surprisingly large number of studies had to be excluded, most commonly because they only reported a significant difference between patients and controls. Six studies used executive or working memory tasks (verbal fluency, N-back, or random number generation); seven used memory tasks (recall or recognition) and one used a vigilance task (the Continuous Performance Task). The total N for these studies was 319.

Figure 6a,b show the combined peak activation foci for schizophrenic patients and controls plotted onto a rendered brain. In both cases wide areas of the prefrontal cortex bilaterally showed significant activation. Comparison of the two distributions in the prefrontal cortex (including the anterior cingulate cortex) revealed no significant difference (KS3 statistic = 0.16, $P = 0.94$). There was also no difference between the remaining non-frontal distributions of peak activation foci (KS3 statistic = 0.14, $P = 0.98$).
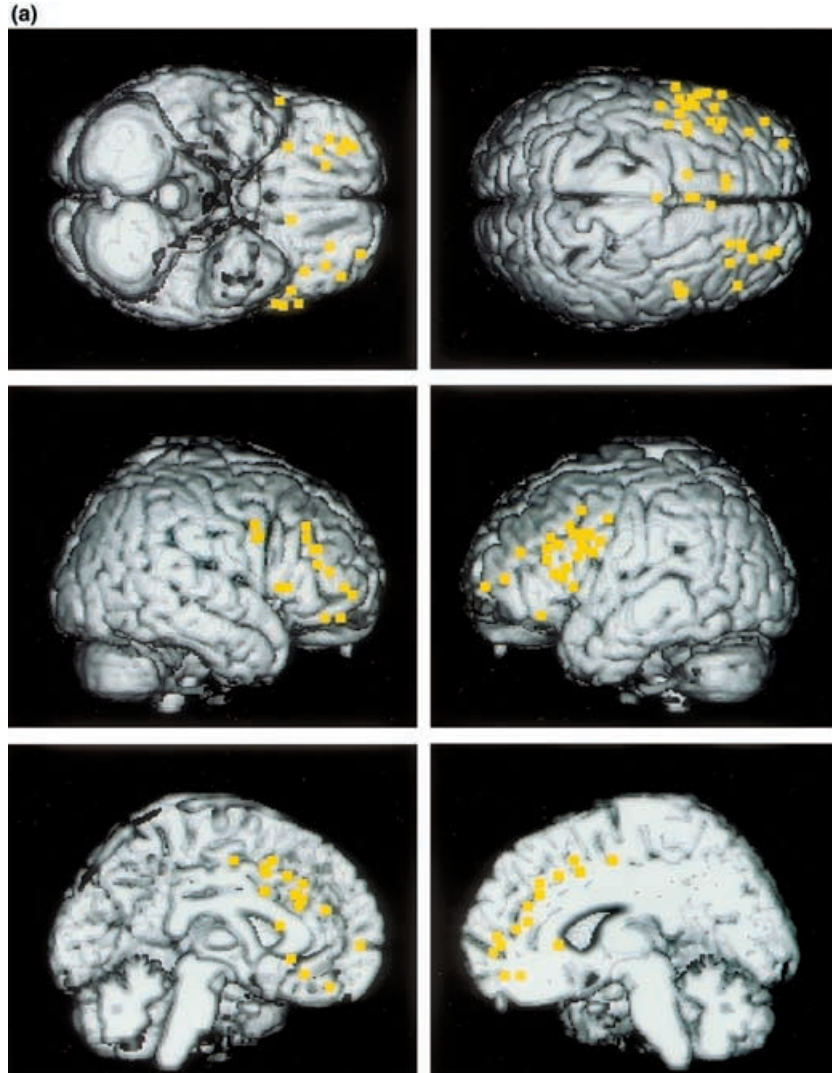

Fig. 5. Relationship between task impairment and hypofrontality in 14 activation studies.

(a)

Fig. 6. Combined peak activation foci for (a) schizophrenic patients and (b) and normal controls from 14 voxel-based studies.

Discussion

In their pioneering functional imaging study Ingvar and Franzen (8) found that whole brain blood flow in schizophrenic patients was not significantly different from that of controls, and did not decrease as a function of duration of illness, a finding which they considered to distinguish the disorder from organic dementia. Whole brain blood flow/metabolism in schizophrenia has attracted little further discussion in the literature, but this meta-analysis tends to support the finding of little overall abnormality. Pooling data from 29 studies resulted in an effect size which fell into the 'small' range and at −0.26 was indicative of only approximately 20% non-overlap between groups. Even this value may have been inflated by publication bias. However, in contrast to Ingvar and Franzen (8), our meta-analysis did find some, albeit not decisive evidence that whole brain blood flow/metabolism decreases in schizophrenia as a function of duration of illness.

Despite the fact that negative findings have been found to equal or even outnumber positive ones (17, 18), this meta-analysis provided robust evidence for the reality of resting hypofrontality in schizophrenia. Analyses of studies using both absolute and relative measures of this revealed effect sizes in the small-to-medium range, with the homogeneous values of −0.32 (relative) and −0.55 (absolute) indicative of an approximately 25–33% non-overlap between patients and controls. These values are smaller than that of −0.65 found in the meta-analysis of Heinrichs et al. (119–121); however, these authors excluded SPECT studies (120), which we found to have a numerically although not significantly smaller effect size than studies using [133]Xenon and PET.

Neuroleptic treatment appeared to be responsible for at least some of the reduction in whole
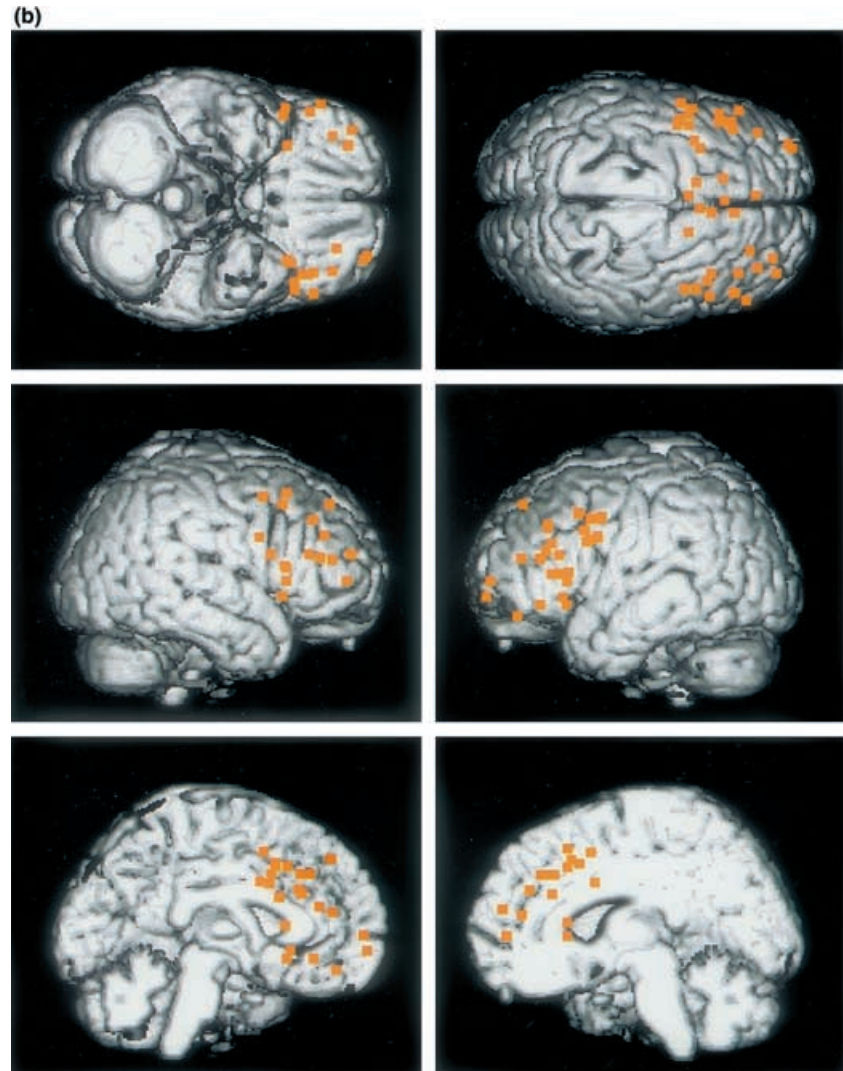
Fig. 6. (Continued)

brain blood flow/metabolism in schizophrenia and was also associated with significantly greater values for hypofrontality in the absolute studies. However, it did not moderate effect size in the studies using relative measures of hypofrontality. A simple – and biological plausible – interpretation of this pattern of findings is that neuroleptics exert a general depressant effect on cerebral blood flow/metabolism. Such a global reduction would tend to increase values for hypofrontality in studies using absolute measures, where flow/metabolism in the frontal regions is simply compared between patients and controls. However, there should be little if any effect in studies using relative measures of hypofrontality because any treatment-induced reduction in frontal flow/metabolism would tend to be cancelled out by the corresponding reduction in whole brain flow/metabolism. Such a simple conclusion stands in contrast to the complex findings in studies which have examined schizophrenic patients before and after treatment with neurolep-

tics. These have found both reductions and no change in whole brain blood flow/metabolism, and reductions, increases, and most commonly no change in frontal values (for a review see 122). However, as well as using both absolute and relative measures of hypofrontality, these studies have sometimes based their findings on administration of single doses of drug, and sometimes on weeks or even months of treatment.

Technique did not significantly influence the effect size for resting hypofrontality, although there was a tendency for SPECT studies to produce smaller values than those using [133]Xenon or PET. SPECT is often considered to be different from [133]Xenon and PET in that, rather than providing a dynamic measure of blood flow over seconds or minutes, it employs radiotracers which become trapped in the brain following initial uptake and accumulate over periods of half an hour or longer. However, FDG PET also shows 'static' characteristics (unlike ordinary glucose it is not rapidly

metabolized by neurones), yet as Fig. 3 indicates there is little to suggest that this technique is associated with obviously smaller values for hypofrontality than the remaining PET studies or the [133]Xenon studies. Some authors have regarded SPECT as being inaccurate (120) or semiquantitative rather than quantitative (123), and while this is not strictly true, as fully quantitative techniques have been developed (124), this point may have some force as most studies on schizophrenic patients have not employed such models.

Heinrichs (120) commented on the marked heterogeneity among the findings for resting hypofrontality in schizophrenia, with some studies producing effect sizes of greater than −1 and others finding small effects in the opposite direction. The examination of moderator variables in our meta-analysis suggests a simple explanation for some of this heterogeneity – that resting hypofrontality in schizophrenia is a function of chronicity of illness. Thus, the pooled effect size in first-episode patients and those with less than 2 years duration of illness was if anything in the direction of hyperfrontality, but as studies included greater numbers of chronic patients hypofrontality became increasingly apparent. If, as this finding suggests, functional brain abnormality in schizophrenia is progressive, it could have important implications for the understanding of the nature of the disorder, because most other biological findings point to neurodevelopmental or at least static brain pathology (2, 125). At the same time, it is important to note that the association with chronicity is confounded by that found with age. Unfortunately, these two variables are difficult to disentangle because the statistical technique used, Rosenthal's focused comparison (27), can only examine one predictor of effect size at a time. Standard multiple regression techniques would also face difficulties due to the high degree of colinearity between age and chronicity, and anyway such techniques are not optimal for meta-analysis as they cannot take the sample size of the individual studies into account.

Meta-analysis also supported activation hypofrontality, with a similar medium effect size to that found in resting studies. At −0.37 in the relative studies and −0.42 in the absolute studies, the effect sizes were again smaller than that of −0.81 found by Heinrichs et al. (119–121) in their meta-analysis. However, as noted above, these authors excluded SPECT studies, and they also included studies using all forms of cognitive tasks, not just those known to engage the prefrontal cortex. In our meta-analysis, few potential moderator variables emerged as significant predictors of effect size. This

failure could of course merely reflect the relatively small numbers of studies (10, 18) in the two analyses. Although numerous further studies have examined the degree of activation of the prefrontal cortex in schizophrenia (for a review see 126), being voxel-based these could not be incorporated into the meta-analysis. For these reasons, activation hypofrontality should probably be regarded as less robustly supported than resting hypofrontality in schizophrenia.

A current controversy in functional imaging research is whether task-related hypofrontality in schizophrenia represents an intrinsic functional brain abnormality – in other words a subtle form of biological lesion – or whether it is merely reflects the fact that schizophrenic patients typically perform cognitive tasks more poorly than normal subjects and so activate their frontal lobes to a correspondingly lesser degree (21, 23). Supporting the former possibility, patients with Huntington's disease (127) and Down's syndrome (128) have been found to show greater prefrontal activation than schizophrenic patients while carrying out the Wisconsin Card Sorting Test, despite being impaired on the task. In favour of the latter possibility, Frith et al. (103) found that when patients and controls were matched for performance by the use of a paced form of verbal fluency task no evidence of hypofrontality was found – although the patients showed impairment on an unpaced form of the task. Meta-analysis supports a relationship between task impairment and activation hypofrontality in schizophrenia, but the finding is not conclusive owing to the limited number of studies and the trend level of significance. Nevertheless, such a result suggests that at the very least performance factors need to be taken into consideration when interpreting functional imaging findings in schizophrenia.

Our combination of voxel-based studies provided little support for the view that schizophrenic patients show a different pattern of activation from normal subjects when they perform of tasks activating the prefrontal cortex. This finding is at odds with that of one recent study (129), which found that schizophrenic patients activated a wider area of prefrontal cortex than normal subjects when performing a working memory task. However, this difference in pattern was not found in another otherwise similar study (130). More broadly, this finding is in conflict with an implicit goal of much current functional imaging research, whose aim has been to demonstrate an altered pattern of regional functional architecture in the disorder. Our finding on this point has to be regarded as provisional since the number of studies

that could be included was small. It may also be argued whether it is legitimate to pool findings from studies using a range of different tasks. However, this approach is defensible because, in their meta-analysis of the pattern of activation in normal subjects, Duncan and Owen (28) found no evidence that different tasks recruited different frontal cortical regions.

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MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

Instruction to printer	*Textual mark*	*Marginal mark*
Leave unchanged	⋯ under matter to remain	Stet
Insert in text the matter indicated in the margin	⅄	New matter followed by ⅄
Delete	⊢⊣ through matter to be deleted	∮
Delete and close up	⇔ through matter to be deleted	∮
Substitute character or substitute part of one or more word(s)	/ through letter or ⊢⊣ through word	New letter or new word
Change to italics	— under matter to be changed	⊔⌐
Change to capitals	≡ under matter to be changed	≡
Change to small capitals	= under matter to be changed	=
Change to bold type	〰 under matter to be changed	〰
Change to bold italic	≋ under matter to be changed	≋
Change to lower case	Encircle matter to be changed	≢
Change italic to upright type	(As above)	⊔⌐
Insert 'superior' character	/ through character or ⅄ where required	γ under character e.g. ⁷γ
Insert 'inferior' character	(As above)	⅄ over character e.g. ₂
Insert full stop	(As above)	⊙
Insert comma	(As above)	,
Insert single quotation marks	(As above)	⌄γ and/or ⌄γ
Insert double quotation marks	(As above)	⌄γ and/or ⌄γ
Insert hyphen	(As above)	⊕
Start new paragraph	⌐	⌐
No new paragraph	⌐⌐	⌐⌐
Transpose	⊔⌐	⊔⌐
Close up	linking ⊃ letters	⊃
Insert space between letters	⅄ between letters affected	#
Insert space between words	⅄ between words affected	#
Reduce space between letters	⌃ between letters affected	⊤
Reduce space between words	⌃ between words affected	⊤