ORIGINAL ARTICLE

Brain Volumes in Relatives of Patients With Schizophrenia

A Meta-analysis

Heleen B. M. Boos, MS; André Aleman, PhD; Wiepke Cahn, MD, PhD; Hilleke Hulshoff Pol, PhD; René S. Kahn, MD, PhD

Context: Smaller brain volumes have consistently been found in patients with schizophrenia, particularly in gray matter and medial temporal lobe structures. Although several studies have investigated brain volumes in nonpsychotic relatives of patients with schizophrenia, results have been inconsistent.

Objective: To determine the magnitude and extent of brain volume differences in first-degree relatives of schizophrenic patients.

Data Sources: A systematic search was conducted to identify relevant studies. Computer searches of the MEDLINE database were performed for English-language articles published before July 2005. Relevant abstracts published in 2005 were also selected.

Study Selection: Magnetic resonance imaging studies that examined differences in brain volumes between first-degree relatives of patients with schizophrenia and healthy control subjects were obtained through computerized databases, including MEDLINE. Studies had to report sufficient data for computation of effect sizes.

Data Extraction: For each study, the Cohen d was calculated. Data extraction and calculation of the effect size were performed by 2 authors (H.B.M.B. and A.A.)who reached a consensus in cases of uncertainty and discrepancies. All analyses were performed using the random-effects model.

Data Synthesis: Twenty-five studies were identified as suitable for analysis and included 1065 independent first-degree relatives of patients, 679 patients with schizophrenia, and 1100 healthy control subjects. The largest difference between relatives and healthy control subjects was found in hippocampal volume, with relatives having smaller volumes than controls (d=0.31; 95% confidence interval [CI], 0.13-0.49; 9 effect sizes). Gray matter was smaller (d=0.18; 95% CI, 0.02-0.33; 7 effect sizes) and third-ventricle volume was larger (d=0.21; 95% CI, 0.03-0.40; 7 effect sizes) in relatives compared with healthy control subjects.

Conclusion: Brain abnormalities are present in nonpsychotic first-degree relatives of patients with schizophrenia and are most pronounced in the hippocampus.

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STRUCTURAL BRAIN ABNORMALITIES are well established in schizophrenia. Several meta-analyses[1,2] have reported smaller brain volumes in schizophrenia, with more pronounced reductions in the hippocampus and amygdala. However, the nature of these brain changes is still unresolved. For instance, whether these changes are a result of the use of antipsychotic medication is a matter of debate.[3-6] Similarly, it is unclear to what extent these abnormalities are related to the vulnerability for developing the illness. Both issues can be (partially) addressed by studying brain structures in relatives of patients with schizophrenia. Clearly, the vulnerability for developing schizophrenia is highly genetic: studies[7] in families of patients with schizophrenia have shown that the origin of the disorder has an estimated heritability of 80%, including interaction between the genes and environment. Thus, the presence of brain changes in relatives of patients would suggest these to be related to the shared genetic risk of developing schizophrenia. Moreover, brain volume differences in relatives cannot be the result of antipsychotic medication. Therefore, examining brain volumes in nonpsychotic first-degree relatives of schizophrenic patients can clarify some of the causes of the brain abnormalities observed in probands.

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In recent years, several studies have measured brain volumes in nonpsychotic relatives of schizophrenic patients compared with those of healthy subjects. Most of these studies[8-16] showed smaller total brain volumes in relatives, but others[17-19] did not. Similarly, larger ventricular volume has been reported in several studies,[14,16,19-22] but 2 other studies did not find this.[12,23] Furthermore, medial temporal lobe structures were reportedly smaller in several studies,[9,17,19,24-27] but this finding has not been universally replicated.[8,11,16,20,28] Thus, although brain abnormalities have been found in first-degree relatives of schizophrenic patients, the findings are inconsistent. Moreover, effect sizes in the individual studies have not been quantitatively reviewed and integrated.

The aim of the present meta-analysis was to determine the magnitude and extent of brain volume differences in first-degree relatives of schizophrenic patients. We attempted to integrate the findings from magnetic resonance imaging (MRI) studies in relatives of patients with schizophrenia. To this end, we examined volumes of global brain structures and smaller structures in nonpsychotic first-degree relatives of patients with schizophrenia compared with those of healthy control subjects. In an additional analysis, we compared brain volumes of patients with those of the unaffected relatives.

METHODS

DATA SOURCES

The MRI studies that examined differences in brain volumes in first-degree relatives of patients with schizophrenia compared with healthy control subjects were obtained through computerized databases, including MEDLINE. The keywords used in the computerized search were *brainabnormalit(s)*, *relative(s)*, and *schizophre(s)*. The terms *relative(s)*, *sib(s)*, *parent(s)*, and *schizophre(s)* were also combined with *brain volume(s)*, *gray matter*, *white matter*, *ventricle(s)*, and *hippocampus*. Titles and abstracts of the articles were examined to see whether or not they could be included. Additional studies were obtained by a hand search of journals published in 2005 that most frequently publish articles on structural brain imaging in schizophrenia to find articles that had not yet been included in computerized databases. The journals included the following: *Archives of General Psychiatry*, *The American Journal of Psychiatry*, *Biological Psychiatry*, *Schizophrenia Research*, *Psychiatry Research: Neuroimaging*, *American Journal of Medical Genetics*, and *Neurobiology of Disease*. Bibliographies of included articles were used for a further search. Finally, abstracts from conferences on schizophrenia presented in 2005 were taken into account.

STUDY SELECTION

Forty-three studies were identified as potential candidates for the meta-analysis. Studies were included if (1) they were MRI studies of brain structures published before July 2005 or they were not yet published but were presented as an abstract at the International Congress on Schizophrenia Research in 2005, (2) they compared first-degree relatives of patients with schizophrenia with a healthy control group (having no history and family history of psychosis), (3) they were published in the English language, and (4) they reported sufficient data to obtain the effect size: means, standard deviations, exact *P* values, or exact F values for a 2-group comparison. Studies in which some of the relatives had an ill family member diagnosed as having schizoaffective disorder (instead of schizophrenia) were also included in this analysis.

Fifteen studies were excluded from the meta-analysis because they did not show relevant data to enable us to compute the Cohen d values.[29-42] Five studies were excluded because they did not report brain volumes of relatives of schizophrenic patients compared with healthy control subjects.[43-47] Twenty-five studies were identified as suitable for our meta-analysis and included 1065 independent first-degree relatives of patients, 679 patients with schizophrenia, and 1100 control subjects. The 25 studies that were identified as suitable reported brain volumes of different types of first-degree relatives; namely, siblings,* monozygotic twins,[10,11,14,16,25,27,49] dizygotic twins,[11,14,25,27,49] parents,[15,17,18,21,28,48,50,51] and offspring.[24] Four studies did not specify first-degree relatives.[8,19,21,26] Together, the 25 studies reported volumes of 56 brain structures. Some of these structures were not evaluated by more than 3 studies, and in this case, these structures were not examined in the analysis. **Table 1** lists the included articles and the brain structures that were analyzed.

DATA EXTRACTION

This meta-analysis was performed to examine measurements of volumes in global brain structures and smaller structures in the medial temporal lobe in nonpsychotic first-degree relatives of schizophrenic patients and healthy control subjects. The structures that were suitable for analysis included total brain, intracranial, lateral ventricle, third-ventricle, gray matter, white matter, amygdala-hippocampal, hippocampal, and cerebrospinal fluid volume. If sufficient data were present, an analysis was performed to examine the effect of the side of the brain and differences in volumes between patients and relatives.

The key to meta-analysis is defining an effect size statistic capable of representing the quantitative findings of a set of research studies in a standardized form that permits meaningful comparison and analyses across the studies.[52] Therefore, for each study in this meta-analysis, the effect size statistic Cohen d was calculated. The Cohen d is the difference between the mean of the experimental group and the mean of the comparison group divided by the pooled standard deviation. In this analysis, the mean volume of a specific brain structure for relatives of patients with schizophrenia was subtracted from the mean volume for comparison subjects and divided by the pooled standard deviation of both. When means and standard deviations were not available, d values were calculated from exact *P* values, *t* values, or F values. Data extraction and computation of the effect sizes were performed independently by 2 of the authors (H.B.M.B. and A.A.). In cases of discrepancies, a consensus was reached by means of discussion. After computing individual effect sizes for each study, meta-analytic methods were applied to obtain a combined effect size, which indicated the magnitude of the association across all studies.[53] Individual effect sizes were inverse variance weighted to correct for upwardly biased estimation of the effect in small sample sizes.[53,54] Additionally, a homogeneity statistic, *Q*, was calculated to test whether the studies could be assumed to share a common population effect size. A significant *Q* statistic indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. If significant heterogeneity is found, a moderator analysis can be performed to investigate the potential moderating factors.[54] A *t* test was subsequently performed on the null hypothesis that the d value is 0.00, which we report together with the associated *P* value.

**References 9, 12, 13, 16-18, 20, 22, 23, 48.*

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Table 1. Summary of 25 Studies in Meta-analysis and Included Brain Volumes

Source	No. of Relatives	No. of Controls	No. of Patients	Included Brain Volumes
Baare et al,[14] 2001	29	58	29	IC, TB, LV, 3V
Boos et al,[15] 2005	66	52	NA	IC, TB, LV, GM, WM, 3V
Cannon et al,[23] 1998	60	56	75	IC, GM, WM
Cannon et al,[13] 2002	51	54	64	TB, GM, WM
Falkai et al,[50] 2004	51	41	45	NA
Gogtay et al,[12] 2003	15	32	NA	GM, WM, LV
Hulshoff Pol et al,[11] 2004	22	44	22	IC, TB, GM, WM
Keshavan et al,[24] 2002	17	22	NA	NA
Lawrie et al,[19] 2001	147	36	34	TB, LV, 3V, AHC
Marcelis et al,[18] 2003	32	27	31	TB, GM, WM
McDonald et al,[21] 2002	96	68	66	TB, LV, 3V
Narr et al,[25] 2002	20	40	20	HC
Narr et al,[48] 2002	20	20	NA	NA
Noga et al,[10] 1996	12	12	12	TB
O'Driscoll et al,[26] 2001	20	14	NA	HC
Schulze et al,[28] 2003	96	68	66	HC
Seidman et al,[22] 1997	6	11	NA	NA
Seidman et al,[51] 1999	28	26	NA	TB, LV, 3V, WM, AHC
Seidman et al,[17] 2002	45	48	18	HC
Sharma et al,[49] 1999	55	39	29	TB
Staal et al,[20] 1998	16	32	16	GM, WM, LV, 3V, HC
van Erp et al,[9] 2002	58	53	72	TB, HC
van Erp et al,[27] 2004	46	109	48	IC, GM, HC
van Haren et al,[16] 2004	32	146	32	TB, LV, 3V, HC
Wood et al,[8] 2005	79	49	NA	TB, HC, NA

Abbreviations: AHC, amygdala-hippocampal complex; GM, gray matter; HC, hippocampus; IC, intracranial; LV, lateral ventricle; NA, not applicable/not available; TB, total brain; WM, white matter; 3V, third ventricle.

According to Cohen,[55] d values of 0.2 show small effects. Values between 0.4 and 0.6 are moderate effects, and d values of 0.8 or higher are large effects. All analyses were performed with a random-effects model using comprehensive meta-analysis.[56] A random-effects model assumes that the true effect size estimated by different studies varies among studies because of differences in samples or paradigms and that these true effect sizes have a normal distribution (ie, heterogeneity exists).[57]

To examine the possibility of publication bias, we computed a fail-safe number of studies.[54,58] Publication bias implies that studies with no effect may not be published, posing a threat to the stability of the obtained effect size. The fail-safe number of studies indicates the number of unpublished studies with null effects that must reside in file drawers to reduce the observed effect size to a negligible level. The statistic can be calculated with the use of the formula given by Orwin[58] and Lipsey and Wilson[52]:

$$k \times [(ES_k - ES_c) - 1].$$

In this formula, k is the number of studies, ES_k, the mean weighted effect size; and ES_c, the criterion effect size (which we set at a d value of 0.10).

DATA SYNTHESIS

The structures that were analyzed, the number of studies included, and the number of subjects in which the structures were measured are reported in Table 1. The composite effect sizes (Cohen d, associated confidence intervals, Q statistics, and P values) of all studies for the different structures are reported in **Table 2**. Only those structures for which the volumes were explored in more than 3 individual studies were analyzed. In applicable studies, brain volumes of patients were also compared with those of relatives.

RESULTS

As presented in Table 2, the results of our meta-analysis indicate brain volume differences between first-degree relatives of patients with schizophrenia and healthy control subjects. The largest effect was found for hippocampal volume, with smaller volumes in relatives compared with healthy subjects (**Figure 1**). In this analysis, 9 studies were included, with a group size of 421 relatives of patients with schizophrenia and 603 healthy control subjects. One of the studies that measured hippocampal volumes controlled for intracranial volume and 8 studies for whole brain volume. The combined-effect Cohen d of the 9 studies was 0.31 ($P<.001$). Excluding the studies that controlled for intracranial volume did not change the results, and analyzing studies (n=12) that measured hippocampal together with amygdala volume even showed a combined-effect Cohen d of 0.52 ($P=.005$). The largest effect was found in left hippocampal volume (d=0.47; $P=.04$; right hippocampal volume: d=0.23; $P=.04$). When we measured hippocampal volume in relatives compared with control subjects, the fail-safe number was 18, large enough to lend credence to our findings.

Small effects were found in cerebral gray matter (smaller in relatives vs healthy control subjects; d=0.18; $P=.04$; fail-safe number=7) (**Figure 2**) and third-ventricle volume (larger in relatives than in healthy control subjects; d=0.21; $P=.02$; fail-safe number=8) (**Figure 3**). The analysis of gray matter volume included 7 studies, with a group size of 249 relatives and 285 healthy control subjects. The analysis of third-

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Table 2. Brain Structures Included in Meta-analysis and Results

Brain Structure	No. of Studies	No. of Relatives	No. of Controls	Mean Weighted Effect Size: Cohen d (95% CI)	Within-Category Homogeneity Statistic (*Q*)	*P* Value for *Q*
Total brain	13	605	633	0.28 (−0.02 to 0.57)	63.99	<.001
Intracranial	8	335	369	0.12 (−0.04 to 0.27)	4.04	.77
Lateral ventricle	7	367	412	0.11 (−0.05 to 0.27)	5.85	.44
Third ventricle	7	414	418	0.21* (0.03 to 0.40)	8.31	.22
Gray matter	7	249	285	0.18* (0.02 to 0.33)	4.68	.70
White matter	7	245	284	0.40 (−0.04 to 0.83)	33.25	<.001
Amygdala-hippocampus	12	605	675	0.52* (0.16 to 0.89)	94.17	<.001
Hippocampus						
Total	9	421	603	0.31* (0.13 to 0.49)	13.79	.09
Left	9	499	444	0.47* (0.34 to 0.61)	6.56	.58
Right	9	499	444	0.23* (0.01 to 0.46)	19.43	.01
Cerebrospinal fluid	4	96	121	0.61 (0.08 to 1.14)	9.81	.02

Abbreviation: CI, confidence interval.
*$P<.05$.

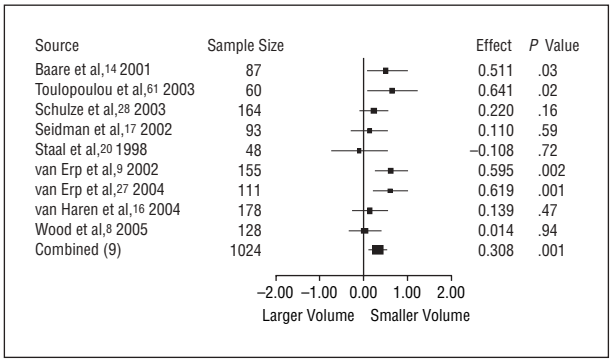

Figure 1. Mean total hippocampal volume. Error bars indicate 95% confidence interval.

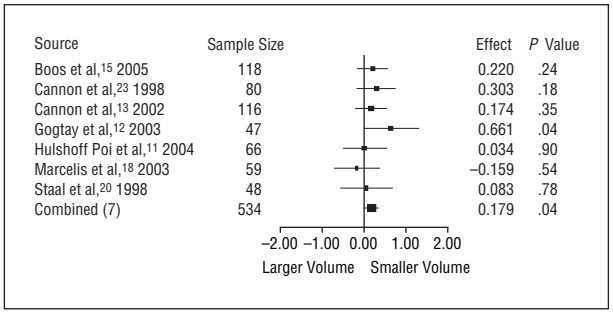

Figure 2. Mean cerebral gray matter volume. Error bars indicate 95% confidence interval.

ventricle volume included 7 studies with 414 relatives and 418 healthy controls. Analyses of volumes of the total brain, intracranial space, lateral ventricles, and white matter did not show significant effects. However, the analysis of total brain and white matter volume showed a trend toward significance (total brain: d=0.28; $P=.06$; white matter: d=0.40; $P=.07$; both smaller in relatives compared with healthy subjects).

Seventeen studies also included a sample of patients (679 patients with schizophrenia and 790 nonpsychotic relatives). Nine studies evaluated the hippocampus among 335 patients and 511 relatives, showing a moderate effect

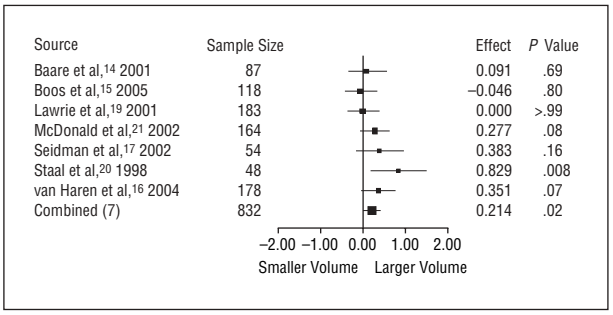

Figure 3. Mean third-ventricle volume. Error bars indicate 95% confidence interval.

(d=0.43; $P=.001$; 95% confidence interval, 0.17-0.68) with patients having smaller hippocampal volumes than relatives. This result showed significant heterogeneity ($Q=22.28$; $P=.004$). However, one study was an outlier, reporting a large decrease in hippocampal volume.[46] When we excluded this study, the heterogeneity was not significant (d=0.29; $P<.001$; $Q=2.67$; $P=.91$). The fail-safe number of studies for this analysis was 29, large enough to lend credence to our findings.

In the analysis that compared first-degree relatives with healthy control subjects, most *Q* values were nonsignificant (Table 2) except for those in the analyses of amygdala-hippocampal complex volume, white matter volume, total brain volume, and cerebrospinal fluid volume. This significant *Q* value indicates heterogeneity of the individual study effect sizes and thus limits reliable interpretation of these results.

COMMENT

This meta-analysis integrated the results of 25 MRI studies that compared brain volumes of 1065 nonpsychotic first-degree relatives of patients with schizophrenia with those of 1100 healthy control subjects. The results indicate that brain volumes in relatives of patients with schizophrenia differ from those of healthy control subjects, with effect sizes in the small to moderate range. The largest effect is found in hippocampal volume (d=0.31), with

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relatives of patients having smaller volumes than healthy control subjects. In addition, total gray matter volume (d=0.18) and third-ventricle (d=0.21) volume are smaller in relatives compared with healthy control subjects. Although total brain and white matter volume did not differ significantly in relatives compared with healthy controls, both structures showed a trend toward significance (P=.06 and P=.07, respectively). The analysis that compared patients with schizophrenia with first-degree relatives showed smaller hippocampal volumes in the patients (d=0.43). In addition, 3 studies that were excluded from this meta-analysis examined hippocampal volumes in first-degree relatives compared with healthy control subjects. Two studies also showed smaller volumes in relatives compared with healthy controls.[32,36] However, Harris et al[33] did not find this.

The results of this meta-analysis suggest that brain abnormalities in schizophrenia are related (in part) to the risk of developing the disease and that these brain changes may therefore predate the clinical onset of the disorder. Moreover, they argue against the notion that the brain abnormalities in schizophrenia are solely caused by antipsychotics. These conclusions are bolstered by the finding that the brain structures affected in relatives are the same as those reported to be abnormal in patients.[2] The findings are supported by 2 studies[59,60] that reported reduced gray matter volumes in similar brain structures of individuals at high risk for schizophrenia. Both studies reported that those relatives who later develop psychotic symptoms have a more severe reduction before the onset of these symptoms.

The finding of hippocampal volume reduction in relatives of schizophrenic patients also dovetails with the results of recent meta-analyses regarding cognitive functioning in relatives.[61,62] In these articles, lower performance in relatives of patients compared with healthy control subjects was reported on several cognitive domains, including verbal and declarative memory, executive functioning, and attention. Interestingly, Sitskoorn et al[62] found that the largest effect size was obtained for verbal memory (d=0.54), being significantly worse in relatives of patients than in healthy subjects. However, the performance of relatives on these cognitive tasks was less impaired than has been reported in patients with schizophrenia.[63,64] Indeed, decreased verbal memory is one of the most robust neuropsychological findings in schizophrenia.[60] Deficits in verbal memory have generally been associated with smaller (left) hippocampal volume,[65] as is also the case in patients with schizophrenia[66,67] and their relatives.[17,26] In the present meta-analysis, the effect size was considerably larger for the left than for the right hippocampus. This finding is consistent with findings from lesion and functional MRI studies in healthy subjects, suggesting more involvement of the left hippocampus in encoding and recognition of verbal as opposed to visual or pictorial material.[68] The suggestion of smaller left hippocampal volume as a vulnerability indicator for schizophrenia, put forward by Seidman et al,[17] is also consistent with these observations.

The findings of this meta-analysis suggest that a common genetic vulnerability to developing schizophrenia is reflected in brain morphologic findings. McDonald et al[69] demonstrated that the genetic risk of schizophrenia is associated with an extensive system of gray matter deficits and white matter abnormalities. However, only a few studies have identified specific genes in relation to brain volume abnormalities in schizophrenia. Szeszko et al[70] studied 19 patients with schizophrenia and 25 healthy control subjects and reported a role for brain-derived neurotropic factor in determining hippocampal volume. More relevant to the finding of the current meta-analysis, Callicott et al[71] examined the effects of the *DISC1* gene on the risk of schizophrenia and its impact on the hippocampus. They found that *DISC1* increased the risk of developing the disease and was also associated with structural and functional alterations in the hippocampus.

However, smaller hippocampal volumes in relatives of patients with schizophrenia could also have been caused by environmental factors. Obstetric complications such as hypoxia are known to result in smaller brain volumes, affecting the hippocampus profoundly.[21,72,73] Smaller hippocampal volumes have also been associated with brain injury[65,74,75] and stress[65,76] and have been found not only in schizophrenia but also in several other psychiatric disorders, such as major depression, posttraumatic stress disorder, obsessive-compulsive disorder, and borderline personality disorder.[65] An important function of the hippocampus and amygdala is the regulation of the hypothalamic-pituitary-adrenal axis, which plays a role in stress processing. This regulation may be altered because of a genetic predisposition. In depression, the hypothalamic-pituitary-adrenal axis is strongly activated and the adrenal cortex hypersecretes glucocorticoids such as cortisol. Although less pronounced, considerable hypothalamic-pituitary-adrenal activation is also found in schizophrenia.[77] On the basis of earlier animal experiments, overexposure to cortisol during prolonged periods of stress is expected to damage the brain, particularly the hippocampus. Sapolsky et al[77] provided evidence in rats that chronic stress, with the concomitant increase in corticoid levels, causes loss of neurons in the hippocampus and subsequent deficits in memory function and cognition. In patients with depression, this glucocorticoid cascade has also been presumed to result in decreased hippocampal volume,[78] possibly explained by apoptosis.[79] Both apoptosis and neurogenesis have been shown to occur in the hippocampus.[80] Thus, smaller hippocampal volumes in patients with schizophrenia and their first-degree relatives might also be the result of stress-related processes in the brain.[81]

These hypotheses regarding putative genetic and environmental factors underlying hippocampal damage in relatives of schizophrenic patients can be integrated by taking gene-environment interactions into account. Gene-environment interactions may result from genetically mediated differences in the sensitivity to environmental factors or environmentally mediated influences on gene expression. Evidence of genetically mediated differences in environmental factor sensitivity shows that slightly elevated rates of obstetric complications are found not only in patients with schizophrenia but also in their nonpsychotic first-degree relatives.[82,83] As reported by Cannon et al,[83] most of these relatives exposed to obstetric complications did not develop schizophrenia, and thus

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these factors are incapable of causing schizophrenia on their own. Obstetric complications may act additively or interactively with genetic factors in influencing liability to schizophrenia. Van Erp et al[9] examined siblings of patients with schizophrenia and found that hippocampal volumes differed stepwise with each increase in genetic predisposition to schizophrenia and that hippocampal volumes of patients exposed to fetal hypoxia were smaller than those who were unexposed, whereas no such relationship was observed within the healthy control subjects. They suggested that carrying susceptibility genes for schizophrenia makes one vulnerable to perinatal damage, especially in the hippocampus.

Some limitations of this meta-analysis should be noted. First, as with all meta-analyses, the results depend on the quality of the individual studies. The adjustment of cerebral structures for whole brain or intracranial volume has been thought to facilitate differences in effects among the studies. However, the results of a moderator variable analysis failed to confirm this hypothesis. Therefore, it is unlikely that the observed differences in volume are due to differences in adjustment.

Second, structures other than those that have been evaluated in this meta-analysis may also be affected in relatives of patients with schizophrenia. The results of smaller hippocampal volumes in relatives compared with healthy control subjects might reflect broader abnormalities in the temporal lobes or even other structures, but because of the small amount of studies that measured these structures, this could not be investigated in our analysis.

Third, the results may have been influenced by publication bias. However, in the present meta-analysis, this is unlikely given a fail-safe number of studies statistic, which indicates the number of studies with null effects that must reside in file drawers before results of the obtained effect sizes are reduced to a negligible level.

Fourth, only a few studies that were included in the meta-analysis and measured brain volumes of siblings specified whether they had used independent samples or multiple siblings per family. Although this may bring in a confounding factor, because of the small number of studies in the meta-analysis, all sibling studies that were available and met the criteria were included.

Fifth, differences in age and sex were not examined. Age and sex are known to affect brain volumes[83]; however, the studies included in this meta-analysis did not provide enough data to examine the effects of age and sex. Except for hippocampal volume, differences between left and right brain structures were not measured. The statistical test to determine the latter results requires left and right regional volumes, and these data were not generally provided by the original studies. Thus, the possibility that some of the effects found in this meta-analysis were caused by confounding factors such as sex and age cannot be ruled out. In addition, some studies[11,48] suggest that white matter reduction reflects an increased risk of developing schizophrenia. Although the present meta-analysis did not find significant decreases, the analysis resulted in significant heterogeneity, which hampers a reliable interpretation and may have influenced the results. More and larger studies are needed to show whether in nonpsychotic relatives total brain and white matter volume differ from healthy control subjects. Longitudinal studies on brain volumes of relatives of schizophrenic patients could also be helpful in diminishing problems of individual study characteristics and reducing heterogeneity issues. In addition, different methods have been proposed for estimating heterogeneity and publication bias. For example, other meta-analyses have included funnel plots (plots of effect estimates against sample size) to index publication bias[84] and the I^2 statistic to measure the proportion of inconsistency in individual studies that cannot be explained by chance. The latter approach was argued to be a better index of heterogeneity than the Q statistic, especially for collections of studies with either small or large sample sizes (measuring inconsistency in meta-analyses).[85] Notably, most studies included in our analyses were of intermediate sample size. Finally, some studies included in this meta-analysis not only studied first-degree relatives but also included some second-degree relatives.[19,21,50] These studies did not examine hippocampal and gray matter volume. However, in the analysis of third-ventricle volume, second-degree relatives were included but the exact amount was not reported in the studies. Excluding the 3 studies that examined some second-degree relatives did not alter the results of our meta-analysis.

In summary, our results provide support for the hypothesis that nonpsychotic first-degree relatives of patients with schizophrenia show structural brain abnormalities, particularly in the left hippocampus. These brain abnormalities are similar to the areas that are affected in patients with schizophrenia and parallel the findings of neuropsychological impairments (especially in verbal memory) in both patients and relatives. Although these findings reflect a vulnerability to developing schizophrenia, it is still unclear how and to what extent genes and/or environment are involved. Future studies should focus on the search for susceptibility genes in relation to brain abnormalities by using linkage and association methods.

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