Published in final edited form as:

Biol Psychiatry. 2005 January 1; 57(1): 83–90. doi:10.1016/j.biopsych.2004.10.014.

Direct and Indirect Effects of Fetal Irradiation on Cortical Gray and White Matter Volume in the Macaque

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Abstract

Background—Schizophrenia is associated with reductions in thalamic neuronal number and cortical gray matter volume. Exposure of nonhuman primates to x-irradiation in early gestation has previously been shown to decrease thalamic volume and neuronal number. Here we examine whether early gestational irradiation also results in cortical volume reduction.

Methods—High-resolution, T1-weighted magnetic resonance scans were collected in adult monkeys 1) exposed to irradiation during the early gestational period (E33-E42) corresponding to thalamic neurogenesis, 2) irradiated in midgestation (E70-81) during neocortical neurogenesis, and 3) not exposed to irradiation. Cortical gray matter and white matter volumes were derived via manual segmentation; frontal and nonfrontal volumes were distinguished via sulcal landmarks.

Results—Monkeys irradiated in early gestation exhibited a trend reduction in nonfrontal gray matter volume (17%) and significant reductions in white matter volume in frontal (26%) and nonfrontal (36%) lobes. Monkeys irradiated in midgestation had smaller gray (frontal: 28%; nonfrontal: 22%) and white matter (frontal: 29%; nonfrontal: 38%) volumes.

Conclusions—The cortical deficits observed in midgestationally irradiated monkeys are consistent with a reduction in cortical neuronal number. Cortical volume reductions following early gestational irradiation may be secondary to reduced thalamic neuronal number and therefore model the thalamocortical pathology of schizophrenia.

Keywords

Frontal; magnetic resonance; neurogenesis; schizophrenia; thalamus

The neuropathology of schizophrenia involves a spectrum of brain regions including the cerebral cortex and thalamus (Jones 1997; Selemon 2001). The majority, albeit not all (Arciniegas et al 1999; Portas et al 1998), in vivo neuroimaging studies have indicated that whole thalamic volume is smaller in schizophrenia subjects relative to control subjects (Byne et al 2001; Csernansky et al 2004; Konick and Friedman 2001), and many other

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studies have detected more localized abnormalities in size, shape, and metabolic activity of the thalamus (Andreasen et al 1994a; Buchsbaum et al 1996; Hazlett et al 1999). Moreover, reduction of thalamic volume is found at early stages of the illness and is not related to antipsychotic drug intake (Ettinger et al 2001; Gilbert et al 2001; Gur et al 1998a). Postmortem stereologic analyses of individual thalamic nuclei have revealed smaller volume and reduced neuronal number in several thalamic nuclei in schizophrenia patients, including the mediodorsal (MD), anterior, ventral lateral posterior, and pulvinar nuclei (Byne et al 2002; Danos et al 2002, 2003; Pakkenberg 1990; Popken et al 2000; Young et al 2000), although not without exception (Cullen et al 2003). Furthermore, analysis of parvalbumin-stained neurons (as a marker for cortical projection neurons) in the anterior nucleus in postmortem brains from schizophrenia patients has shown that these neurons are selectively reduced in number (Danos et al 1998). Parvalbumin-stained axon terminals in the middle layers of the dorsolateral prefrontal cortex, thought to be the termination of thalamic projection neurons located in MD, are also decreased in schizophrenia subjects (Lewis et al 2001). Together, these findings suggest that thalamocortical projections to the association cortices represent a major site of pathology in schizophrenia.

Structural neuroimaging analyses also have indicated that cerebral cortical gray matter volume is smaller in widespread areas of the cerebral mantle in schizophrenia patients (Harvey et al 1993; Zipursky et al 1992), and some evidence from magnetic resonance (MR) scanning (Andreasen et al 1994b; Goldstein et al 1999; Nopoulos et al 1995; Sullivan et al 1998) suggests that the gray matter volume deficit may be disproportionately large in frontal regions in schizophrenia. Smaller frontal gray matter volume in schizophrenia is not a universal finding in the imaging literature, however (for reviews, see McCarley et al 1999; Shenton et al 2001; Yurgelin-Todd et al 1996), and McCarley et al (1999) have suggested that the magnitude of the deficit (8%–15%) is at the limit of resolution for detection with current neuroimaging analyses, leading to both positive and negative results. Until recently, postmortem analyses of the frontal lobe had failed to find smaller gray matter volume in schizophrenia (Highley et al 2001; Pakkenberg 1993; Thune et al 2001); our stereologic study, which was limited to the left hemisphere and included only nonaged subjects, uncovered a 12% deficit in frontal gray matter volume in schizophrenia patients (Selemon et al 2002). In contrast, few studies have found smaller cortical white matter volume in brains from schizophrenia subjects (Breier et al 1992); most find selective sparing of white matter in the disease (Sanfilipo et al 2000; Selemon et al 2002; Sullivan et al 1998; Zipursky et al 1992).

The coexistence of schizophrenic pathology in the thalamus and cortex, brain regions that are highly and specifically interconnected, raises the possibility that abnormalities in one area may be causally related to a primary defect in the other. In this study, fetal irradiation was used as a tool to disrupt neurogenesis in the nonhuman primate. Because of the prolonged gestational development of the primate brain, thalamic and neocortical populations undergo their final mitotic division at different prenatal ages, allowing for selective deletion of neurons in the thalamus and the cortex (Ogren and Rakic 1981; Rakic 1974, 1976, 1977). Accordingly, we have exposed monkeys to x-irradiation either during the period of thalamogenesis or during the period of neocortical neurogenesis and examined the consequent effects on cortical volume in these animals when they had reached full maturity

in comparison with a group of adult monkeys that had not been exposed to irradiation. The objectives of this study were to determine whether monkeys that were irradiated in early gestation would exhibit a cortical volume deficit like that described for schizophrenia patients (Andreasen et al 1994b; Harvey et al 1993; Selemon et al 2002; Sullivan et al 1998; Zipursky et al 1992) and to compare the cortical deficit produced by early gestational irradiation with that resulting from midgestational irradiation that specifically targeted cortical populations.

Methods and Materials

Thirteen adult macaque monkeys were analyzed in this study (Table 1). Three had been exposed to x-irradiation during the period of thalamogenesis (E33-42) in early gestation (eFIM); three had been irradiated in midgestation (mFIM) when neocortical neurons are generated (E70-E81), and seven were nonirradiated control animals (CON). The irradiation protocol has been described in detail previously (Algan and Rakic 1997). The exact time of exposure and dose of irradiation is shown in Table 1. Animals were imaged at 5–9 years of age and therefore were young adults. Full maturity in a macaque monkey is reached at approximately 4.5 years; aging processes begin in the late teens. All experimental procedures were approved by the Institutional Animal Care and Use Committee.

MR Acquisition and Preparation

High-resolution MR scans were acquired on a 1.5-Tesla LX GE Advantage scanner located at Yale University School of Medicine. A T1-weighted, spoiled gradient recalled acquisition at steady state (SPGR) sequence (repetition time = 25 msec, echo time = 4 msec, flip angle = 30¡, acquisitions = 124, matrix 256 × 256) was used to collect these scans, which provided a voxel resolution of .625 mm × .625 mm × .7 mm (.7 mm coronal thickness and back-filled to .625 mm × .626 mm per slice) across the entire cranium. The skull in the MR image was removed using an automated brain extraction program (Sandor and Leahy 1997; Shattuck et al 2001).

Delineation of Frontal–Nonfrontal Boundaries

Anatomically, the frontal lobe was separated from the parietal lobe posteriorly by the central sulcus, between the ventral-most tip of the sulcus and the dorsal-most tip at the supramedial margin of the hemisphere. Ventrally, the frontal lobe was separated from the temporal lobe by the Sylvian fissure. The posterior limiting point of the Sylvian fissure in its horizontal traverse was defined as a point anterior to the upward curve of the fissure, and the anterior limiting point of the Sylvian fissure was defined as that portion that bordered the temporal lobe.

Segmentation of Cortical Gray and White Matter

The MR image of the entire cranium was manually segmented into white matter (WM), cortical gray matter (GM), subcortical gray matter (e.g., thalamus and basal ganglia), and cerebrospinal fluid (CSF). The brain stem and cerebellum were excluded. Subcortical GM and CSF were excluded from all subsequent image processing and statistical analyses. This manual delineation was done by two of the authors (LW and MBN) using Analyze software.

To extract frontal and nonfrontal cortical voxels, we first created a surface at the GM–WM interface using a triangulation method (Miller et al 2000; Ratnanather et al 2001). The frontal lobe subsurface (enclosed by the central sulcus and the Sylvian fissure, see the anatomic description provided earlier) was then extracted using a the method described in Khaneja et al (1998) and Ratnanather et al (2003). The GM and WM voxels that projected into this subsurface area (by locating the closest surface point to each voxel) then constituted the frontal lobe GM and WM, respectively. The same procedure was repeated to extract the nonfrontal lobe subsurface from the volume posterior to the central sulcus and Sylvian fissure. Volumes were determined by summing the respective voxels and then multiplying the sums by the voxel dimensions.

To test the repeatability of the extraction procedure, frontal lobe GM and WM volumes were extracted a second time by one of the authors (LW). The intraclass correlation coefficients of the frontal-lobe cortical GM and cortical WM volumes were .99 and .91, respectively.

Statistics

Because of the small sample size, ranks of frontal GM and WM and nonfrontal GM and WM volumes were used in the statistical analysis (i.e., without Gaussianity parameterization). If two subjects' volumes were the same, their ranks would be the same and would take on the same fractional values (e.g., rank orders of 4, 5.5, 5.5, 7 instead of 4, 5, 6, 7). To test for group differences in GM and WM, analysis of variance (ANOVA) was performed across all three groups on the ranks with post hoc comparison between eFIMs and CONs and between mFIMs and CONs (SAS, version 8.01). Post hoc tests determined whether the leastsquared means of the experimental groups were significantly smaller than that of the normal control subjects (one-tailed *t* tests). Rank-correlation tests were performed to assess the relationship between age and frontal GM, frontal WM, nonfrontal GM, and nonfrontal WM. Preliminary analysis using a rank correlation test indicated that age was not correlated with any of the volume variables, and therefore age was not included as a covariate in the ANOVA.

Results

Frontal Lobe Gray Matter

Frontal lobe GM volume in eFIMs was reduced by 13% compared with control subjects whereas that of mFIMs was 28% smaller than control animals (Figure 1, Table 2). There was a significant group effect ($F_{2,10}$= 5.57; p = .024) for GM (ranks). Post hoc comparison revealed that GM in mFIMs was significantly reduced compared with control animals; the difference in GM volume between eFIM and CON was not significant (Table 2).

Frontal Lobe White Matter

Frontal lobe WM was reduced by 26% in the eFIMs and by 29% in the mFIMs compared with control animals (Figure 1, Table 2). There was a significant group effect ($F_{2,10}$= 15.47; p = .0009) for WM (ranks). Post hoc comparison indicated that the reductions in both irradiated groups were significant (Table 2).

Nonfrontal Lobe Gray Matter

Nonfrontal lobe cortical GM volume in eFIMS was reduced by 17% compared with control animals, and that of the eFIMs was reduced by 22% (Figure 1, Table 3). There was a trend group effect ($F_{2,10}$= 3.91; p = .056) for nonfrontal lobe cortical GM (ranks). Post hoc comparisons revealed that nonfrontal lobe cortical GM in mFIMs was significantly reduced compared with control animals, with a trend reduction in the eFIMs (Table 3).

Nonfrontal Lobe White Matter

In the posterior cortical lobes of eFIMs, WM volume was reduced by 36% compared with control animals, whereas that of the mFIMs was reduced by 38% (Table 3). There was a significant group effect ($F_{2,10}$= 15.07; p = .001) for nonfrontal WM (ranks). Post hoc comparisons revealed that nonfrontal WM in both eFIMs and mFIMs was significantly reduced compared with control animals (Table 3).

When total cerebral volume was included as a covariate in the ANOVA, none of the differences between groups for frontal and nonfrontal volumes was significant. These findings probably reflect the fact that cortical volume represents a large proportion of total cerebral volume and also indicate that the changes in brain volume include subcortical structures as well.

Discussion

Monkeys that were exposed to irradiation in midgestation, when cortical neurons are undergoing final mitosis, exhibited pronounced deficits in cortical GM volume undoubtedly reflecting a substantial reduction in cortical neuronal number in these animals. Early gestational irradiation resulted in a more modest decreases in cortical GM volume in the posterior (nonfrontal) lobes and in the frontal lobe where the reduction did not reach significance although the magnitude (13%) of the reduction in frontal GM volume was in the range (8%–15%) found for frontal GM volume reduction in patients with schizophrenia (McCarley et al 1999; Selemon et al 2002). Monkeys irradiated at either gestational age exhibited a pronounced reduction in cortical WM volume, suggesting that cortical connectivity is diminished by irradiation exposure at either time point.

Thalamic volume and neuronal number in the MD have previously been studied in these same irradiated monkeys. Monkeys irradiated in early gestation were shown to have significantly smaller thalamic volumes (Schindler et al 2002; Selemon et al 2003b) and significantly fewer neurons in the MD nucleus (Selemon et al 2004) and in the whole thalamus (Selemon et al, unpublished observations) than nonirradiated control animals whereas thalamic volume and MD neuronal number were not different from controls in monkeys irradiated in midgestation. As the primate frontal lobe receives a robust projection from the thalamus and particularly from MD (Goldman-Rakic and Porrino 1985; Ray and Price 1993), the modest and nonsignificant reduction in volume of the frontal lobe to some extent may be attributed to a reduction of thalamic projections to the frontal cortex. These conclusions must be considered tentative pending replication in a larger sample of monkeys, however.

Limitations and Possible Confounds of the Study

One limitation of this study is the small number of fetally irradiated animals available for study. If larger numbers of animals had been available, increasing the statistical power of the analysis, the frontal and nonfrontal GM volume deficits observed in animals that had undergone early gestational irradiation might have reached significance. A new cohort of fetally irradiated monkeys has been created that may eventually be added to this data set, but these animals are still 2–4 years from reaching full maturity.

A related technical consideration is that the effect of the irradiation exposure may be nonuniform across subjects. For example, of the three early gestationally irradiated monkeys, two had reduced (29%, 17%) frontal cortical GM volumes relative to mean control frontal GM volume, whereas frontal GM volume in the third was similar to the control mean. In this same animal, stereologic cell counting of the thalamus indicated that neuronal number in the whole thalamus and in the mediodorsal nucleus of the thalamus was similar to nonirradiated controls (Selemon et al 2004). These findings, although preliminary given the small number of subjects, suggest that reduction of cortical gray matter volume is dependent on effective elimination of thalamic neurons by the early gestational irradiation. When comparable data are available from the new cohort of early gestationally irradiated monkeys, it may be possible to determine whether thalamic neuronal number is correlated with cortical gray matter volume in these animals.

The total dose of irradiation was greater in the animals irradiated in midgestation than in those exposed in early gestation (see Table 1), and therefore it is possible that the greater reduction in cortical gray matter volume observed in animals irradiated in midgestation was due to a dose effect; however, analyses of thalamic volume and neuronal number in these same animals revealed a significant decrease only in the early gestationally irradiated animals despite the fact that these animals had received less exposure to irradiation (Schindler et al 2002; Selemon et al 2004). These findings indicate that brain pathology is not simply greater overall because of the higher dose of irradiation received by the midgestationally irradiated group. Indeed, Algan and Rakic (1997) examined infant monkeys that were irradiated at similar prenatal ages with comparable doses of irradiation and found that irradiation in early gestation resulted in large reductions in neuronal number in the lateral geniculate nucleus (LGN) and relatively modest decreases in neuronal number in the primary visual cortex. Conversely, midgestational irradiation reduced cortical neuronal number while sparing the LGN. Thus, at the doses administered in this experimental paradigm, timing rather than dose of exposure to irradiation is the critical factor in determining which structures are most severely affected.

Another possible limitation of this study is that the brain volumes were not corrected for intracranial volume. We elected instead to examine the results with and without covarying for total cerebral volume. Because the experimental manipulation occurred prenatally, intracranial volume should correlate closely with total cerebral volume since the head expands during childhood and adolescence to accommodate the growing brain. Enlargement of the extracerebral spinal fluid space occurs only in adult degenerative disorders when the brain atrophies after reaching maximal size. Although correction for head size or intracranial volume has become the norm in neuroimaging studies of human disease, several studies that

have given careful consideration to this issue have concluded that such a correction could be counterproductive when studying developmental disorders (e.g., Arndt et al 1991; Mathalon et al 1993).

When ANOVAs were performed with total cerebral volume (ranks) as a covariate, differences across groups were not significant. These analyses suggest that neither irradiated group exhibits a selective reduction of cortical volume but rather that the cortical volume deficit is proportionate to reduction of whole brain volume in the fetally irradiated monkeys. This is not surprising because animals exposed to early gestational irradiation would have reduced subcortical neuronal number and volume and animals exposed to midgestational irradiation would have reduced cortical neuronal number throughout the cerebral mantle, not just in the frontal lobe. It is noteworthy that GM deficits observed in schizophrenia patients are not specific to the frontal lobe although some studies indicate that they are more prominent in the frontal lobe; widespread volumetric reductions have been found throughout the cerebral mantle and in large subcortical structures including the thalamus and neostriatum (McCarley et al 1999; Zipursky et al 1992).

Direct and Indirect Effects of Fetal Irradiation

X-irradiation is lethal to dividing cells (Han and Elkind 1977, 1978), and therefore the direct effect of exposure to x-rays prenatally is reduction of neuronal number in those structures that are undergoing final mitosis. Brain structures that have already completed all mitotic divisions will be unaffected by the irradiation. Structures in which mitosis is ongoing will lose progenitor cells; however, the survivor population of progenitor cells will undergo many additional generations of divisions, and therefore these populations will be able to recover and produce normal numbers of neuroblasts. As a result, the specificity of irradiation for targeting certain populations of neurons is based on the timing of irradiation exposure in relationship to the temporal sequence of neurogenesis in the developing brain as established by tritiated thymidine labeling studies (Brand and Rakic 1979, 1980; Levitt and Rakic 1982; Rakic 1974, 1976, 1977; Rakic and Nowakowski 1981). Thus, the impact of irradiation delivered in midgestation when cortical cells are generated on cortical volume is presumably a direct effect of reduction of cortical neuronal number. In contrast, the effect of early gestation irradiation on cortical volume is most likely an indirect effect related to reduction of neuronal number in subcortical structures, such as the thalamus, that are highly interconnected with the cortex, and therefore the result of neuropil reduction rather than to deletion of neurons.

In this regard, quantitative analyses in the visual system have established that neuronal number in structures that are closely connected is genetically determined and independently regulated. For example, the correlation between numbers of neurons in the retinal ganglion and its thalamic relay the LGN, as well as between the LGN and the primary visual cortex, is surprisingly weak (Seecharan et al 2003; Suner and Rakic 1996). The independence of neuronal number in LGN and visual cortex is congruent with Algan and Rakic's (1997) observations that a substantial reduction of thalamic neuronal number in early gestation did not result in comparable cell death in the cortical target population.

Early Gestational Irradiation in the Primate: A Model for Schizophrenia?

We have become interested in the early gestationally irradiated animals as a model for cortical pathology in schizophrenia because a previous study indicated that irradiation during the embryonic period of thalamogenesis produced anatomic alterations in the primary visual cortex that resemble those observed in schizophrenia patients (Algan and Rakic 1977; Selemon et al 1995). Specifically, following early gestational irradiation neuronal density in granular (IV) and infragranular (V, VI) layers of primary visual cortex was increased, whereas cortical thickness was not significantly altered. Morphometric studies over the past decade have uncovered a similar elevation in neuronal density in the primary visual cortex and in the dorsolateral prefrontal cortex in schizophrenia (Selemon et al 1995, 1998, 2003a), and these findings have been interpreted to indicate that interneuronal neuropil, the compartment that consists of processes and connections between cells, is reduced in the disease (Selemon and Goldman-Rakic 1999). Consistent with the reduced neuropil hypothesis, many studies have reported decreased complements of synaptic proteins, dendritic spines, and axonal markers in the cortex in schizophrenia subjects (for review, see Selemon 2001). Our findings in this study further characterize the cortical deficit in early fetally irradiated monkeys and show that early gestational irradiation produced a reduction of frontal gray matter volume in two of the three monkeys examined and that the reduction was similar in magnitude to that observed in schizophrenia patients (McCarley et al 1999; Selemon et al 2002). Studies are currently underway to investigate the cellular basis of this volumetric reduction and to determine whether neuronal loss or neuropil reduction accounts for the volumetric changes.

Monkeys irradiated during either early gestation also showed substantial reductions in frontal white matter whereas reduced cortical white matter volume has not been observed in most studies of schizophrenic patients (Sanfilipo et al 2000; Selemon et al 2002; Sullivan et al 1998; Zipursky et al 1992). These findings indicate that the pathology in the early fetally irradiated monkey, although similar in many respects to the neuropathology of schizophrenia, does not faithfully replicate all features of the anatomic phenotype of schizophrenia. There are several possible explanations for this discrepancy. The decreases in thalamic volume and neuronal number resulting from the early gestational irradiation protocol that we used may be greater in magnitude than those found in schizophrenia and result in larger decrements in thalamocortical axons in the white matter. Indeed, recent studies have indicated that total thalamic volume is reduced by only about 5% in schizophrenia patients and that the decrease is proportionate to that of whole brain volume (Csernansky et al 2004; Konick and Friedman 2001), whereas the thalamus was approximately 25% smaller in early gestationally irradiated monkeys compared with nonirradiated control animals, and the reduction was disproportionately larger than that of whole brain volume (Schindler et al 2002; Selemon et al 2003b). The issue is not entirely clear, however, because postmortem studies of individual thalamic nuclei have reported reductions in volume ranging from 9% to 30% (Byne et al 2002; Danos et al 2002, 2003; Pakkenberg 1990; Young et al 2000).

Another possibility is that the decrease in white matter volume in early gestationally irradiated monkeys is due to deleterious effects on other subcortical and allocortical brain

structures. Neurogenesis in neural structures, including the subiculum, neostriatum, hippocampus, and brain-stem monoamine neuronal cell groups, temporally overlaps the period of thalamogenesis in the macaque (Brand and Rakic 1979, 1980; Rakic 1974; Rakic and Nowakowski 1981; Levitt and Rakic 1982); therefore, exposure to irradiation in early gestation most certainly curtailed neurogenesis in widespread areas of the brain and may have secondarily resulted in significant white matter volume reduction. The relative lack of specificity associated with early gestational irradiation, however, mirrors in many respects the widespread pathology of schizophrenia because many of the same structures affected by exposure to irradiation in early gestation (e.g., the hippocampus, the neostriatum, and monoaminergic systems) have been implicated in the pathophysiology of the disease (Akil et al 1999, 2000; Csernansky et al 1998, 2002; Keshavan et al 1998; McCarley et al 1999; Nelson et al 1998; Shenton et al 2001). Nonetheless, fetal irradiation probably produced more severe pathologic deficits in volume and neuronal number in subcortical and allocortical areas compared with the relatively subtle neuropathologic abnormalities described in schizophrenia, and these gray matter decrements may in turn have resulted in white matter volume reduction, an abnormality that is not generally observed in brains from schizophrenia patients.

Finally, other factors that have not been modeled in the fetally irradiated monkey but are thought to play a role in the pathophysiology of schizophrenia, such as genetic determination of brain size (Baare et al 2001; Cannon et al 2002; Lawrie et al 2001; Sharma et al 1998; Steel et al 2002), perinatal complications (Lewis and Murray 1987; McNeil et al 1994), and neurodegenerative processes (DeLisi et al 1997; Gur et al 1998b; Mathalon et al 2001; Woods et al 1996), most likely contribute to the pattern of anatomic abnormalities observed in schizophrenia patients. Differences in the pathology of the fetally irradiated nonhuman primate and that of schizophrenia patients may reflect an interaction between prenatal reduction of neurogenesis and one or more of these other processes.

Interestingly, one of the early gestationally irradiated monkeys in this study was tested on the spatial Delayed Response Task (DRT), which uses the working memory capacity of the prefrontal cortex (Castner et al 1996) and exhibited an adultonset deficit in performance on this task. In infancy, the early gestationally irradiated monkey’s performance was comparable to that of nonirradiated control monkeys. As adults, the control monkeys’ performance on the DRT improved, whereas the irradiated monkey’s performance worsened, and in fact this monkey was no longer able to perform the task at the longest delay interval tested. These results, although intriguing, are preliminary and need to be replicated in a larger sample.

Effects of Irradiation Exposure in Humans

Two events in the past century have resulted in exposure of human populations to high doses of irradiation: the atomic bombing of Japanese cities during World War II and the 1986 Chernobyl nuclear reactor disaster in the Ukraine. Although prenatal exposure following the atomic bombings has not been shown to cause an increase in the incidence of schizophrenia, embryonic irradiation did have deleterious effects on cognitive function and mental health. Atomic radioactivity is more damaging to human tissues than x-irradiation and therefore

may have more global consequences on brain development. For example, an increase in severe mental retardation, increased seizure disorders, and decreased head size were observed in individuals whose mothers were 8–25 weeks pregnant during the bombings, and gestational weeks 8–15, a period corresponding to the end of the first trimester and the beginning of the second trimester of pregnancy, was identified as a particularly vulnerable period for prenatal irradiation exposure (for review, see Otake et al 1991). Likewise, children exposed in utero to radiation from the Chernobyl reactor at 8–25 weeks of gestation exhibited a multitude of developmental abnormalities, including disturbances in electroencephalographic (EEG) patterning, decreased IQ, language disorders, and behavioral and emotional abnormalities (Loganovskaja and Loganovsky 1999). Of course, these children have yet to pass through the age of onset for schizophrenia, so it is not presently known whether they will manifest an increased incidence of schizophrenia in later life. Interestingly, adults who were exposed to very high levels of radiation from the Chernobyl incident had a fourfold higher occurrence of schizophrenia relative to the general Chernobyl population, and adults exposed to moderate to high doses exhibited an increase in the incidence of schizophreniform disorders (Loganovsky and Loganovskaja 2000). The latter findings suggest that very high levels of radiation may have lethal effects on neuronal populations even in the fully mature brain that can trigger a schizophrenialike illness.

Relevance to the Neurodevelopmental Hypothesis of Schizophrenia

Epidemiologic studies of human populations have established that a variety of relatively mild and nonspecific prenatal insults (e.g., maternal infection, malnutrition, and fetal Rh incompatibility) are associated with an increased incidence (about twofold) of schizophrenia in adulthood (Brown et al 2000; Hollister et al 1996; Mednick et al 1988; Susser and Lin 1992; Susser et al 1996). Although our understanding of the disturbances in developmental mechanisms that account for the increase in schizophrenic phenotype is currently quite limited, available evidence suggests that the immune response to maternal infection, rather than the infectious agent itself, is responsible for the higher incidence of schizophrenia because specific cytokines (tumor necrosis factor alpha, interleukin-8) have been found to be elevated in maternal serum samples from schizophrenic patients (Babulas et al 2003; Buka et al 2001). Furthermore, in rodent cell culture, cytokines have been shown to regulate the survival of embryonic neurons (Jarskog et al 1997; Marx et al 2001). Therefore, neuronal genesis and survival in early gestation are processes that might be vulnerable to maternal immune attack secondary to infection or Rh incompatibility. Likewise, maternal malnutrition and associated vitamin deficiency may indirectly have adverse effects on neuronal viability by reducing fetal levels of neurotrophic factors (Eyles et al 2003). Thus, although prenatal exposure to irradiation has not been directly implicated in the etiology of schizophrenia, reduction of neuronal number in the fetal brain may be a common denominator in several prenatal perturbations that increase the risk for schizophrenia.

Acknowledgments

This research was supported by National Institutes of Health Grant Nos. MH62130 (JC), MH071616 (JC), MH59329 (LS), and MH44866 (PGR). We thank Dr. Michael I. Miller, Johns Hopkins University, for providing the geodesics-based subsurface extraction tool (BrainWorks). We also Heidi Voegeli and Gary Leydon, Yale University, for technical help and for electronic transfer of files.

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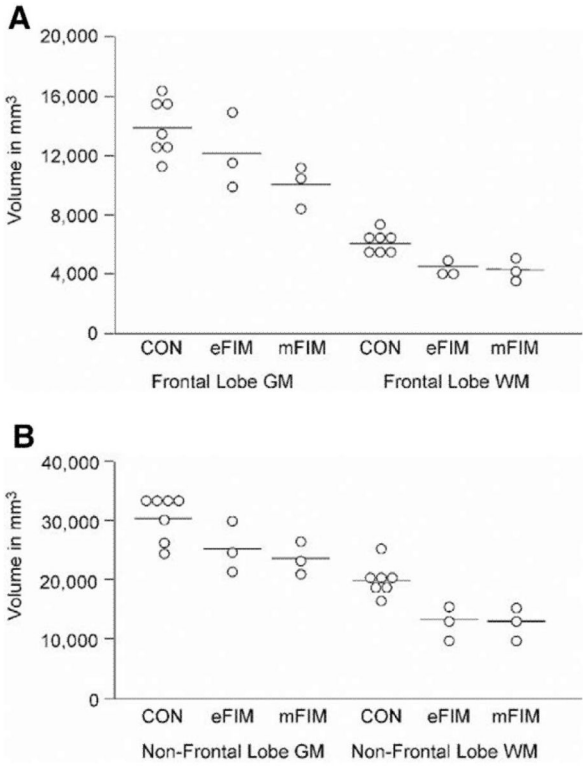

Figure 1.

In the top graph, frontal lobe gray matter (GM) and white matter (WM) volumes for each animal are plotted. Mean volumes for nonirradiated control animals (CON), early gestationally irradiated monkeys (eFIM), and midgestationally irradiated monkeys (mFIM) are indicated by bars. Lower graphs shows individual volumes of nonfrontal lobe GM and WM.

Table 1

Irradiation Exposure and Dose

Animal	Sex	DOB	Age at MR Scan (Years)	Time (E) and dose (cGy)	Total Dose (cGy)
eFIM1	M	010595	5.5	E33(25), E35(50), E37(50), E41(50)	175
eFIM2	M	020295	5.42	E33(50), E35(50), E36(50), E37(50)	200
eFIM3	F	051893	6.75	E35(50), E37(50), E39(50), E42(50)	200
mFIM1	M	091791	8.17	E73(100), E74(100), E75(100)	300
mFIM2	M	091791	8.17	E73(100), E74(100), E75(100)	300
mFIM3	F	040491	9.25	E70(100), E72(100), E75(100) E77(100), E79(100), E81(100)	600
CON1	M	031592	7.92		0
CON2	M	080895	7.25		0
CON3	M	070994	8.75		0
CON4	F	091295	7.17		0
CON5	F	032595	8.71		0
CON6	F	081492	8.33		0
CON7	F	031394	8.54		0

CGy, centigrays; CON, Control monkey; DOB, date of birth; E, embryonic day; eFIM, early fetally irradiated monkey; F, female; M, male; mFIM, midgestationally fetally irradiated monkey; MR, magnetic resonance.

Table 2

Frontal Lobe Volumes in FIM and CON Monkeys

Group	Cortical Gray Matter[a]	Statistic[b]	White Matter[a]	Statistic[b]
CON	13,916 (1,911)		6,088 (688)	
eFIM	12,089 (2,555)	$t = -1.62$ $p = .12$	4,494 (558)	$t = -4.24$ $p = .0016$
mFIM	10,005 (1,397)	$t = -3.27$ $p = .0081$	4,341 (720)	$t = -4.70$ $p = .0008$

CON, control monkey; eFIM, early fetally irradiated monkey; mFIM, midgestationally fetally irradiated monkey.

[a] Mean volume (SD) in mm^3.

[b] Post-hoc one-tailed comparisons on least-squared means of ranks: eFIM vs. CON; mFIM vs. CON.

Table 3

Nonfrontal Lobe Volumes in FIM and CON Monkeys

Group	Cortical Gray Matter[a]	Statistic[b]	White Matter[a]	Statistic[b]
CON	30,279 (3,684)		19,800 (2,799)	
eFIM	25,028 (4,366)	$t = -2.09$ $p = .058$	12,707(3,024)	$t = -4.31$ $p = .0015$
mFIM	23,587 (2,598)	$t = -2.40$ $p = .035$	12,309(2,462)	$t = -4.54$ $p = .0010$

CON, control monkey; eFIM, early fetally irradiated monkey; mFIM, midgestationally fetally irradiated monkey.

[a] Mean volume (SD) in mm^3.

[b] Post hoc one-tailed comparisons on least-squared means of ranks: eFIM versus CON; mFIM versus CON.