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Citation

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The Brain in Schizotypal Personality Disorder: A Review of Structural MRI and CT Findings

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Abstract

Studies of schizotypal personality disorder (SPD) are important because the condition is genetically related to schizophrenia and because data accumulating to confirm its biological underpinnings are challenging some traditional views about the nature of personality disorders. This review of 17 structural imaging studies in SPD indicates that individuals with this disorder show brain abnormalities in the superior temporal gyrus, parahippocampus, temporal horn region of the lateral ventricles, corpus callosum, thalamus, and septum pellucidum, as well as in total cerebrospinal fluid volume, similar to those seen in persons with schizophrenia. Differences between SPD and schizophrenia include lack of abnormalities in the medial temporal lobes and lateral ventricles in SPD. Whether the normal volume, and possibly normal functioning, of the medial temporal lobes in individuals with SPD may help to suppress psychosis in this disorder remains an intriguing but still unresolved question. Such speculation must be tempered due to a paucity of studies, and additional work is needed to confirm these preliminary findings. The imaging findings do suggest, however, that SPD probably represents a milder form of disease along the schizophrenia continuum. With further clarification of the neuroanatomy of SPD, researchers may be able to identify which neuroanatomical abnormalities are associated with the frank psychosis seen in schizophrenia.

Although schizophrenia was once considered the "graveyard of neuropathologists,"[1] recent neuroimaging techniques have radically changed this view. Early studies using computerized tomography (CT) were pivotal in demonstrating ventricular abnormalities in the disorder but did not provide the resolution required to document alterations in regions with unclear boundaries such as the amygdala and various thalamic nuclei. With the advent of magnetic resonance imaging (MRI), these latter brain regions of interest have been evaluated in schizophrenia and found to be abnormal. In recent comprehensive reviews[2,3] of MRI-documented morphological brain abnormalities in schizophrenia, most brain regions studied showed neuroanatomical alteration compared with the same regions in healthy controls. Nonetheless, a convergence of findings suggested that the major locus for brain abnormalities was the temporal lobe; fewer studies reported abnormalities in the lateral ventricles, prefrontal cortex, inferior parietal cortex, basal ganglia, thalamus, corpus callosum, or septum pellucidum.[2,3] Note that, although many regions are involved in schizophrenia, they do not appear to be equally affected, and the temporal lobe regions are the most severely altered. (For

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a recent review of MRI findings in schizophrenia and a discussion comparing the various brain regions, see Shenton and colleagues.2)

In many cases, however, these MRI findings are difficult to interpret, given the possible confounding effects of the chronicity of the psychotic illness and the medications used to treat it. Although the definition of a personality disorder4 requires that a person experience distress, the stress of chronic psychosis as seen in schizophrenia is arguably more relentless. McEwen and Margarinos[5] have demonstrated that increased stress-induced adrenal cortisol release, along with excitatory amino acids, may result in atrophy of the hippocampal CA3 region. Such atrophy may help to explain some of the medial temporal lobe findings in schizophrenia (see section on temporal lobe structures, below).

Medications can also affect brain morphology. Chakos and colleagues[6,7] compared the volume of the basal ganglia in patients taking traditional and atypical antipsychotics and found that the traditional antipsychotics increased caudate volume more than did the atypical medications. Other possible effects of medication on brain morphology have been reported for superior temporal gyrus volume.[8] In addition, a recent animal model[9] demonstrated increased volume and glial density in the prefrontal cortex with chronic exposure to conventional neuroleptics. The effect of anticholinergics, benzodiazepines, and anticonvulsants on specific brain regions has been less extensively examined.

One way to avoid the possible confounding effects of medication is to study patients during a first episode of schizophrenia, before they are treated with medications,[10–15] as well as to investigate at-risk populations,[16] including first-degree relatives of individuals with schizophrenia.[17–23] An alternative approach is to study other populations presumed[*] to have similar genetic vulnerability, such as patients with schizotypal personality disorder (SPD). Our review will focus on CT and MRI structural imaging studies of persons with SPD.

SPD is characterized by difficulties with social interaction and language, together with odd behavior and magical thinking. Because individuals with this disorder are not considered psychotic, they have generally not been prescribed medications. Nonetheless, persons with SPD and those with schizophrenia have a similar genetic predisposition, as suggested by multiple family studies[24,27–31] reporting that 6–7% of individuals diagnosed with schizophrenia have a first-degree relative with SPD. Similarly, first-degree relatives of persons with SPD have a 6.9% chance of developing schizophrenia.[27]

In an early epidemiological study conducted in Denmark, Kety and colleagues[29] found that the data supported the notion of a commonality between schizophrenia and schizophrenia-like disorders, and they grouped these conditions into the "schizophrenia spectrum disorders." This work was followed by Kendler and colleagues' Roscommon County family studies,[27,30] which further supported the spectrum concept and encouraged the use of other research tools to define the phenotypic similarities between SPD and schizophrenia.

Other methodologies such as neurochemical analyses, behavioral studies, and neuropsychological and evoked-potential measures have also shown abnormalities in SPD that are similar to what has been demonstrated in schizophrenia.[32] These include elevated homovanillic acid levels,[33,34] aberrant eye-tracking,[35–38] reduced prepulse inhibition,[39] cognitive deficits,[40–43] and electrophysiological abnormalities.[44–48] One hypothesis that attempts to incorporate findings from these various methodologies has been proposed by Siever (personal communication), who stated that the relative sparing in terms of symptoms and

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[*]"Presumed," since the underlying defective gene-gene interactions in schizophrenia have yet to be elucidated, although population studies have supported the contention that schizophrenia and SPD share a common genetic diathesis (see below).[24–28]

biological abnormalities in SPD compared with schizophrenia may be due to the fact that hypodopaminergic function emanates from the basal ganglia and extends to the frontal lobes. These projections may be "neuroprotective" to other regions such as the frontal lobes.[32,49] Structural MRI studies of the basal ganglia and frontal lobes as well as functional studies examining dopaminergic function are needed to test this hypothesis further.

Another impetus for studying SPD, in addition to the disorder's close genetic and biological ties with schizophrenia, is the importance of such research for the conceptualization of personality disorders. More specifically, personality disorders have traditionally not been thought to have a neurological basis. Now a wealth of data from multiple sources is radically challenging this view (see the studies cited in the previous paragraph). Moreover, with the neuroanatomical basis of SPD becoming more clearly established, investigations of the biological underpinnings of SPD may be a useful model to apply to other personality disorders.

The critical question that we ask, and seek to answer, in this review is: Do the imaging data support the notion that SPD is a less severe version of schizophrenia, or is it a distinct disorder? If the former, might we expect that persons with SPD will have fewer neuroanatomical abnormalities, and therefore less-severe clinical symptoms, than do individuals with schizophrenia? If the data support the idea that SPD is a less penetrant form of schizophrenia, then the next question concerns what abnormalities are present in schizophrenia but absent in SPD. Answers to this last question need to be examined in future studies and may help to direct attention to strategies for preventing the development of schizophrenia.

We performed a *Medline* search in February 2001 for English-language articles including the key words *schizotypal personality disorder, schizophrenia, relatives, computerized tomography*, and *magnetic resonance imaging*. We found and reviewed 17 studies. We began with investigations in which subjects met full DSM criteria for SPD, then continued with studies in which subjects had some of the features of SPD but did not meet the full criteria, reports of children with symptoms consistent with SPD, and finally other studies (i.e., reports of persons with SPD and schizophrenia analyzed together, or of individuals with SPD who have family members with schizophrenia). This organization reflects the different strategies used by researchers to enlist subjects with SPD for their studies. Such strategies include recruiting families of probands with schizophrenia, recruiting patients from clinics, recruiting community dwellers by means of newspaper advertisements, and recruiting college students who score high on scales of psychopathology thought to tap cognitive manifestations of SPD. Diagnostic criteria have also differed and range from meeting five out of the nine required DSM-IV criteria, to having some features of schizotypy derived by diagnostic impression during clinical interview, to scoring high on scales of psychopathology.

We included all 17 studies in our review, even though some included very few patients with SPD or SPD-like pathology. Table 1 provides a summary of these studies.

OVERVIEW

Two important changes have occurred over time in brain morphology studies of individuals with SPD. First, CT techniques have gradually given way to MRI, which has allowed the investigation of more regions and with finer neuroanatomical resolution (including differentiation between gray and white matter). Second, researchers have gone from examining subjects with some features of schizotypy to studying persons determined through semistructured interviews to meet full DSM criteria for SPD. This change can been seen in Table 1, where it is clear that the majority of recent studies use MRI and involve subjects meeting full criteria for SPD.

All eight of the MRI studies that analyzed the data for subjects with full criteria separately have emanated from two centers, Mt. Sinai School of Medicine[49–52] and Harvard Medical School. [53–55] (Note that in 1992 and 1994 researchers from the University of Pennsylvania[56,57] used CT to examine a cohort of subjects who met full criteria for SPD, considered under the category of subjects at high risk for schizophrenia [all had mothers with the disorder].) This illustrates not only the difficulty in recruiting this important subject population but also the fact that different laboratories employ different approaches for understanding the intrinsic morphological abnormalities of the brain found in the schizophrenia spectrum disorders. Importantly, however, nine of the 17 studies were published since 1998, suggesting a marked increase in interest in this topic.

STUDIES OF SUBJECTS WHO MEET FULL CRITERIA FOR A DIAGNOSIS OF SPD

Two laboratories investigating SPD have used individuals who meet full DSM criteria for the diagnosis of SPD. The two laboratories have employed distinctly different recruitment procedures, however. The first laboratory, at Mt. Sinai School of Medicine, has recruited its subjects from local inpatient and outpatient units. Some of these individuals have received medications, including neuroleptics. Our laboratory at Harvard Medical School and the Veterans Affairs Boston Healthcare System, by contrast, has recruited subjects from the community by means of newspaper ads and posted fliers so as to avoid the potential confounding effects of medication. The use of such disparate approaches may have resulted in the sampling of quite different populations. This fact, plus differences between the clinical assessment protocols in the two laboratories, makes direct comparisons between the study populations difficult. The Mt. Sinai cohort, for example, may include subjects with either more-serious symptoms or a greater proportion of positive symptoms, leading them to attend a clinic and be prescribed neuroleptic medications; our cohort may include subjects with a greater proportion of negative symptoms, or with fewer or more-attenuated symptoms. All of this is conjecture, however, since neither group has reported measures of positive and negative symptoms. In addition, neither group of researchers has discussed the potential issue of high Axis I and Axis II comorbidity, which has been described by McGlashan.[58] This may be an important focus for future work on the biological basis of SPD. These different approaches may be complementary in that they may help to elucidate how clinical features affect brain morphology. Note that, as with other studies included in this review, the number of subjects studied in these laboratories is limited, and within a laboratory, samples have partially overlapped. This reflects the difficulties inherent in recruiting subjects with SPD. However, since researchers are just beginning to understand the neuroanatomy of SPD, extensive study of various brain regions in a limited number of subjects may be a prudent approach.

Below, we review findings from Mt. Sinai on the thalamus and corpus callosum. We then review findings from our laboratory on cerebrospinal fluid (CSF), gray and white matter, temporal lobe structures, and the cavum septi pellucidi, and finally the findings from both laboratories on the lateral ventricles.

Mount Sinai Group: Clinic-Based Studies

Thalamus—The thalamus is the major relay station of the brain; it consists of multiple nuclei and their connections to cortical regions (i.e., mediodorsal nuclei with the prefrontal cortex, and anterior and midline nuclei with limbic and paralimbic structures[59]). Due to these interconnections, the thalamus is considered by some to be key to the understanding of schizophrenia.[60]

The first study of thalamic volume in subjects with SPD, conducted by Hazlett and colleagues, [51] showed no differences in thalamic volume or thalamus:brain ratio between patients with SPD and controls but did show differences in shape. Patients with SPD had fewer pixels in the right mediodorsal nucleus and patients with schizophrenia had fewer pixels in the left anterior region than did controls. In a second component of the study, the investigators determined with positron emission tomography that patients with schizophrenia had diminished metabolism in the mediodorsal nucleus bilaterally compared with SPD patients and comparison subjects.

To refine these findings further, Byne and colleagues[52] examined the pulvinar and mediodorsal nuclei of the thalamus in a subset of the subjects. They reported that, compared with controls, both the patients with SPD and those with schizophrenia had reduced pulvinar nuclei, but the patients with schizophrenia had the additional abnormality of reduced mediodorsal nuclei. Various subdivisions of the pulvinar are involved in relaying sensory inputs to primary visual and auditory sensory areas,[59] to the prefrontal cortex,[52] and to the temporoparietal heteromodal association cortex.[52,61] There are a few reports of damage to this region resulting in language disturbances.[51,60] Thus, these nuclei may be critically involved in the processing and integration of visual and auditory information, and damage could hypothetically result in misperceptions.

Taken together, these results suggest that frontolimbic/thalamic connectivity may be different in SPD than in schizophrenia, and this may, in part, contribute to the differences in the clinical symptoms in the two disorders. Such a possibility is particularly interesting, given the current interest in thalamic connections and, as proposed by Andreasen and others,[60] their possible central role in the production of these conditions.

Corpus callosum—The corpus callosum is the major interhemispheric fiber pathway. One of the theories of the etiology of schizophrenia[62] involves a failure of interhemispheric communication. As a result, the corpus callosum has been the subject of 27 investigations; 17 of these have reported abnormalities.[2] In the only study to examine corpus area and shape in SPD, Downhill and colleagues[49] reported that the genu of the corpus was larger in patients with SPD than in those with schizophrenia or control subjects, whereas the posterior corpus was largest in controls, second largest in patients with SPD, and smallest in patients with schizophrenia. (The difference in the latter measure between SPD patients and schizophrenia patients was not statistically significant, however.) Furthermore, these investigators found that the shape differences were consistent with the differences in corpus area. They concluded that these area and shape abnormalities of the corpus may lead to poor interhemispheric connectivity and could be responsible for the improper reality testing found in the schizophrenia spectrum disorders.

Our Laboratory: Community-Based Studies

CSF, gray, and white matter—In many studies of patients with schizophrenia, there appears to be an abundance of CSF, whether measured in the ventricles, in the sulci, or as total CSF volume.[2,3] In our sample of individuals with SPD, we demonstrated increased CSF volume that was not attributable to lateral ventricle enlargement. We also examined total gray matter volume and found no difference between persons with SPD and normal controls. However, when the cortical gray matter was more carefully delineated with the elimination of the subcortical structures and the cerebellum, we found a trend toward reduced cortical gray matter in persons with SPD compared with controls.[55] We found no difference in white matter between the two groups.

Temporal lobe structures—Interest in temporal lobe structures in schizophrenia stems from the critical role of these structures in language and auditory processing and the observation

that language abnormalities and auditory hallucinations are among the hallmarks of this disorder. Of note, many independent research laboratories investigating schizophrenia have reported abnormalities in temporal lobe structures,[2,3,63–67] including the superior temporal gyrus (STG), parahippocampal gyrus, and amygdala-hippocampal complex. The volumes in these regions have also been correlated with cognitive and clinical symptoms including formal thought disorder and auditory hallucinations, as well as with verbal memory problems.[62,68] The amygdala, more specifically, may be involved in the attaching of emotional relevance, particularly to visual stimuli including emotional facial expressions;[69] in general arousal and other basic functions including sleep, feeding, and sexual activities;[68] and in memory.[68]

Our own laboratory[70] has reported reductions in gray matter volume in the STG, amygdala, hippocampus, and parahippocampal gyrus in persons with schizophrenia, and we have extended this work to patients with first-episode psychosis[71] and individuals with SPD. We applied the methodology of our previous studies in schizophrenia to a group of individuals with SPD recruited from the community by means of newspaper advertisements. We predicted that we would see similar, but more-attenuated, volume reduction in the subjects with SPD. We found such subjects to have selective reduction of the left STG gray matter and parahippocampal asymmetry.[54] In an attempt to refine the STG results, we examined two of its main components, Heschl's gyrus and the planum temporale,[72] and found the former to be reduced. In addition, we found that subjects with SPD exhibited formal thought disorder.[54] This was intriguing, since reduced STG gray matter is one of the most robust findings in schizophrenia (all of the 12 studies examining this found volume reduction[2]), and parahippocampal asymmetry has been shown postmortem to be abnormal in persons with schizophrenia.[73] This study demonstrating partial—but not complete—replication suggested that perhaps, at least in this region, there is a relationship between volume affected and clinical severity.

Cavum septi pellucidi—The septum pellucidum is a membrane formed in utero by two leaflets that fuse secondary to pressure of the growing hippocampus and corpus callosum. Space remaining when the closure is incomplete is termed "cavum septi pellucidi"; such a space is seen in 15% of healthy controls[52] at 6 months.[53] The presence of a large cavum septi pellucidi has been noted in schizophrenia (11 out of 12 studies reported abnormalities).[2] One study[53] has examined this neurodevelopmental abnormality in patients with SPD, and it found a prevalence of 27%. These data suggest that SPD and schizophrenia probably have a neurodevelopmental component to their etiology.

Clinic- and Community-Based Studies: Lateral Ventricle Findings

The two laboratories have each examined the lateral ventricles in patients with SPD. They produced slightly different results in the anterior and temporal horns, possibly due to different demographic variables.

Historically, enlarged lateral ventricles have been one of the most common findings in the schizophrenia literature: 78% of the 55 MRI[2] studies (as well as 75% of the CT studies[2]) examining this region showed larger lateral ventricles in persons with schizophrenia than in controls. However, neither the Mt. Sinai group (first with CT[74] and then with MRI[50]) nor our group[55] has found a statistically significant difference in total lateral ventricle volume between individuals with SPD and controls. Thus, in this region there appears to be a difference between schizophrenia and SPD: persons with SPD are less affected than are those with schizophrenia.

Subtle differences may exist between persons with SPD and healthy controls in particular regions of the lateral ventricles, however. In an evaluation of clinic-based SPD patients at Mt. Sinai, Buchsbaum and coworkers[50] reported that the left anterior and temporal horns in these individuals were larger than those in age- and sex-matched normal controls but significantly

smaller than those in patients with chronic schizophrenia. This contrasts with what our laboratory has shown in our community-based sample, in which we reported no difference. [55] Therefore, although both groups report no statistically significant difference between persons with SPD and controls, the Mt. Sinai study included the additional feature of comparing such volumes with those of schizophrenia patients and demonstrated a continuum among the three groups on this measure.

These two studies were similar in that they both involved subjects meeting full criteria for SPD, but they differed in demographic variables. Left- and right-handed males and females were included in Buchsbaum and colleagues' investigation,[50] whereas only right-handed males were included in Dickey and coworkers' study.[55] Perhaps the greatest difference in the samples, however, results from the method of recruitment—clinic versus community. Subjects in a clinic-based sample may have more-severe SPD symptoms than do those in a community-based one; they may also have fewer negative symptoms such as social anxiety. The issue of high Axis I and Axis II comorbidity, which has been described in SPD[58] but is not addressed in these publications, may also be important in deciphering the findings. In addition, pharmacological treatment of SPD patients could be playing a role in clinic-based samples. These variables may be key in understanding the subtle differences in the findings concerning the anterior and temporal horns.

In summary, these two MRI studies of subjects who met full criteria for SPD did not show enlarged lateral ventricles. This may suggest that in individuals with pure SPD this region is spared the abnormalities typically seen in persons with schizophrenia. Subsequent studies to examine the lateral ventricles either have analyzed SPD patients together with schizophrenia patients or have not used subjects clearly diagnosed with SPD (see below). One tentative conclusion, therefore, is that enlargement of the lateral ventricles is not a feature of SPD, and the presence of enlarged ventricles in schizophrenia may be a morphological index of clinical severity.

OTHER STUDIES

Studies of Subjects with Schizotypal Features Who Meet Some but Not All Criteria for a Diagnosis of SPD: Frontotemporal Area

One approach to understanding the schizophrenia spectrum disorders is to study individuals who do not meet criteria for a particular disorder but who nonetheless have some of the features of that disorder. This approach is best exemplified by Raine and coworkers,[75] who examined 17 subjects who scored high on scales of schizotypal features but were not assessed using DSM criteria. These individuals were employees of local hospitals and other work settings. Excluded from the pool of perspective subjects were physicians and other workers expected to have high social class and a high level of education. In this study high degrees of schizotypy were found to be significantly associated with reduced left prefrontal area and with left and right prefrontal:temporal area ratios. The prefrontal cortex is involved in impulse inhibition, assessing the behavioral relevance of stimuli, using working memory while shifting sets, making judgments, and planning. It has vast interconnections with most other sections of the cortex and can influence the activation or de-activation of those areas.[59] Unfortunately, the imaging protocol was performed on a machine with low magnetic field strength (0.15 T, as opposed to the 1.5 T often used), and only one slice was used to determine prefrontal and temporal areas for each subject. Nonetheless, this early study suggested that persons with some schizotypal features may have aberrations in the prefrontal and temporal cortices— areas that have been shown to be abnormal in individuals with schizophrenia.

An excess of schizotypal traits in subjects with a sex chromosome aneuploidy (SCA) was documented in a recent thesis.[76] To follow up on this observation, Warwick and

colleagues77 studied individuals with SCA and some features of schizotypy. Using MRI to examine multiple brain regions including the prefrontal cortex, they detected no abnormalities. Unfortunately, data for the subjects with SCA and many features of schizotypy were not analyzed separately from data for those with SCA alone.

Given the paucity of prefrontal studies examining subjects who have been clearly diagnosed with SPD, no firm conclusions can be drawn for this brain region.

A Study of Children at Risk for Developing SPD or Schizophrenia: Amygdala, Temporal Cortex, and Corpus Callosum

In the only relevant study of children, Hendren and colleagues[78] reported that 8- to 12-year-olds with symptoms of either SPD or schizophrenia showed reduced amygdala and temporal cortex volumes and reduced corpus callosum area, similar to what has been shown in schizophrenia.[2,3] The authors suggested that the occurrence of abnormalities at a young age is the result of genetic or environmental events occurring in utero and altering neurodevelopment; they did not explore other possible etiologies, such as postnatal stress. Hendren and coworkers did not demonstrate enlarged lateral ventricles, as has been shown in subjects meeting full criteria for SPD.[50,55] Instead, they hypothesized that enlarged ventricular volume may represent disease progression in schizophrenia, a speculation shared by others,[79,80] but because the study was cross sectional, their data did not address that issue directly. Due to the subjects' young age, the investigators were unable to make definitive distinctions between SPD and schizophrenia, so subject groups were not analyzed separately. As suggested by the authors, it will be interesting to follow these children and retrospectively review their scans to determine whether the children who subsequently developed SPD had quantitatively fewer abnormalities than did those who subsequently developed schizophrenia.

A Study Analyzing Patients with SPD and Those with Schizophrenia Together: Ventricles

In a hospital-based study of patients with SPD or schizophrenia who also had prodromal symptoms of obsessive-compulsive disorder (OCD), persons with nonpsychotic OCD, and normal controls, Kurokawa and coworkers[81] examined MRIs to determine whether the presence of enlarged ventricles might promote the early detection of SPD or schizophrenia in persons who early in the course of the illness show symptoms of OCD. They found that the patients who had developed SPD or schizophrenia had larger ventricles than did those with OCD alone. They concluded that patients with OCD symptoms and enlarged ventricles on MRI may be at risk for later developing one of the schizophrenia spectrum disorders. They did not analyze data for the SPD patients separately, however, probably due to the small sample size (n = 4). Conclusions about ventricular size in SPD cannot be drawn from this study, since the subjects with schizophrenia may have been driving the findings.

Studies of Patients with SPD Who Have First-Degree Relatives with Schizophrenia: Ventricles

The Mt. Sinai group, in search of genetic markers common to schizophrenia spectrum disorders, has studied family pedigrees of probands with schizophrenia. Within these families, some members have been affected by SPD. Shihabuddin and colleagues[82] studied a family with the linkage marker for such disorders on the short arm of chromosome 5(5p14.1–13.1). Eleven family members (of whom three had schizophrenia and two had SPD) underwent CT to determine whether there was a relationship between the presence of the marker and brain abnormalities. All of the affected members and one unaffected member carried the marker allele. These six individuals had enlarged lateral ventricles and an enlarged ventricle:brain ratio (VBR), whereas the remaining unaffected members did not.

Silverman and colleagues[83] have shown increased VBR in persons with SPD or schizophrenia in a larger group of families. In this study, however, the researchers lumped the individuals with SPD together with family members who had four of nine criteria for the disorder but not full-blown SPD. How the persons with full criteria differed from those with partial criteria was not detailed. Nonetheless, the investigation suggested a relationship between the genetic loading and brain structure.

Prior to the publication of DSM-III, persons with features consistent with SPD (for example, subtle thought disorder, social isolation, magical thinking) were classified as having borderline schizophrenia.[84] Today, many of these subjects would be reclassified by DSM-IV criteria as having SPD. In an early CT study of offspring of mothers with schizophrenia, Schulsinger and coworkers[84] found that the offspring with schizophrenia had enlarged third ventricles and an increased VBR, whereas the mentally healthy offspring had normal ventricles, and those with borderline schizophrenia had the smallest ventricles. This is the only study in our review that reported smaller ventricles in subjects with an SPD-like disorder than in controls. In addition, the offspring with schizophrenia had experienced more obstetrical complications than had either of the other two groups. These authors[84] suggested the "diathesis-stress" model for interpreting the data—that is, that "schizophrenia is the result of deleterious environmental influences acting on a genetic predisposition."

In a second CT study of offspring of mothers with schizophrenia, Cannon and colleagues[57] found that the offspring suffering from SPD or schizophrenia had enlarged sulci, but only those with schizophrenia had enlarged ventricles. (The study also included offspring of unaffected mothers. Some of these offspring had psychiatric disorders, and some did not. The four offspring with SPD who had unaffected mothers were not analyzed separately.) These researchers concluded that the offspring with the more-severe disorder, schizophrenia, had more morphological abnormalities (sulcal and ventricular enlargement), whereas those with SPD had sulcal enlargement alone. Previously these researchers[56] had demonstrated that offspring of mothers with schizophrenia (healthy, with SPD, or with schizophrenia) had enlarged third ventricles, but unfortunately they did not perform analyses comparing the three groups.

DISCUSSION

It is difficult to reach conclusions from such a limited number of studies composed of small sample sizes and subjects with disparate characteristics. Nonetheless, from studies with subjects who meet full criteria for SPD, it appears that individuals with SPD may have reduced gray matter of the superior temporal gyrus, asymmetry of the parahippocampus, abnormalities in thalamic shape and pulvinar volume, larger sulci, abnormalities in the shape of the corpus callosum, and a high prevalence of large cavum septi pellucidi. Each of these potential abnormalities has been well documented in schizophrenia.[2,3] In most of the studies, however, the subjects with SPD do not have all of the abnormalities that might be present in schizophrenia. For example, persons with SPD have reduced superior temporal gyrus volumes and parahippocampal asymmetry but not the frank parahippocampal volume differences or differences in other medial temporal lobe structures such as the hippocampus and amygdala that are found in schizophrenia (see above). Also, from the studies done to date, lateral ventricles appear to be normal.

The specific pathogenesis of these morphometric alterations in SPD cannot be determined from the studies reviewed. For example, one cannot deduce whether the abnormalities are a direct result of neurodevelopmental genetic programing, whether they are a result of distal abnormalities causing deafferentation, or whether they represent a decrease in interneurons.

Byne and colleagues,[52] in their discussion of thalamic abnormalities, proposed the possibility of different etiologies for different nuclei within the thalamus.

To determine whether the additional regions affected in schizophrenia are critical for the production of frank psychosis (i.e., whether they are also present in affective disorder with psychosis) or are inherent to schizophrenia, data from our laboratory comparing affective disorder with psychosis is informative. Table 2, a comparison among SPD, first-episode schizophrenia, and first-episode psychotic affective disorder,[71] shows that the development of psychosis may require abnormalities in the medial temporal lobe structures. This is in contrast to the involvement of the superior temporal gyrus, the increase in sulcal CSF, and the decrease in cortical gray matter found in both SPD and schizophrenia, but not in first-episode psychosis. These patterns of abnormalities suggest that the superior temporal gyrus may be critical in the schizophrenia spectrum disorders.

To return to our earlier question of whether SPD should be considered a distinct disorder or a subset of schizophrenia, we believe that the CT and MRI data produced so far cannot fully separate the two conditions. To date, there has been no definitive report of an SPD abnormality that has not been shown in schizophrenia.[†] In fact, one of the strategies of SPD research is to examine brain regions that have been found to be abnormal in schizophrenia to determine whether they may represent abnormalities fundamental to the schizophrenia spectrum disorders or to psychosis. Once other brain regions are examined, additional abnormalities may be found. However, based on the available literature, one can conclude that not all the abnormalities found in schizophrenia are found in SPD. For example, medial temporal lobe structures are normal in SPD.[54] Therefore, SPD may be considered to represent an attenuated form of schizophrenia.

The implication of these findings is that individuals with SPD are comparatively spared in some brain regions while those with schizophrenia are relatively afflicted, despite possibly similar genetic diatheses. It may be, however, that this genetic continuum can result in some subjects having more of a critical genetic load and others having less. Additionally, subtle in utero differences such as lower incidence of exposure to influenza virus—or less stress-induced steroid release—in persons with SPD than in those with schizophrenia may account for the differences in the development of the two disorders. Finally, as these individuals age, repeated environmental stressors may have an additional impact on the progression of both SPD and schizophrenia. How sparing or affliction occurs is critical to determine in future studies.

We believe that SPD represents part of the continuum of clinical symptoms observed in the schizophrenia spectrum and involves some of the same morphological abnormalities. Conservatively speaking, however, the available CT and MRI data cannot rule out the possibility that SPD is a distinct disorder, although this possibility seems unlikely. One primary strategy of SPD research is to examine brain regions that have been found to be abnormal in schizophrenia to determine whether or not they are also observed in SPD or are a nonspecific concomitant of psychosis. One example of the separation between SPD and psychosis is demonstrated by the finding that medial temporal lobe structures (the amygdala and hippocampus) are abnormal in first-episode schizophrenia and in first-episode psychosis[71] but not in SPD.[54]

[†]There are two possible exceptions. Downhill and colleagues[49] reported corpus callosum shape differences in certain regions in persons with SPD. The corpus has been shown to be abnormal in schizophrenia,[2] although perhaps in slightly different regions. Also, Hazlett and colleagues[51] found fewer pixels in the region of the right mediodorsal nucleus in patients with SPD than in those with schizophrenia or normal controls.

FUTURE DIRECTIONS

Clearly more studies are necessary to investigate the neuroanatomy of SPD. Persons who meet full criteria for SPD need to be evaluated, and this population, although difficult to tap, is important to our understanding of which brain abnormalities are inherent to the schizophrenia spectrum and which are due to the ravages of schizophrenia and its treatments—or perhaps to other prenatal or environmental stresses. The relationship among genetic load, pre- and postnatal environmental factors, and morphological abnormalities in the development of schizophrenia is far from clear. Nonetheless, understanding the interaction of these factors is critical for understanding the pathogenesis of schizophrenia and potential avenues for intervention.

This review focused on CT and structural MRI findings in SPD. Morphological studies can describe volumes, shapes, and anatomical patterns but cannot address the critical question of the functional capacity of the structures. To date, no functional MRI (fMRI) studies of SPD have been published. As more laboratories move toward fMRI and begin to elucidate the functional anatomy of this disorder, it will be important to discover how individuals with SPD differ from those with schizophrenia in the realms of attention, language processing, and emotional processing/expression, where some of the core abnormalities in the schizophrenia spectrum are seen. This complementary coupling of morphometric and functional studies can then begin to address the relationship between anatomy and clinical phenomena. For example, if one believes that magical ideation and certain delusions represent clinical phenomena along a continuum of severity, then fMRI experiments involving subjects with SPD or schizophrenia who are experiencing magical ideation or delusions, respectively, may help to sort out the anatomy involved in those two phenomena. Such an experiment may point to specific areas of functional impairment in the brains of these individuals. However, interpreting findings of a reduced fMRI signal is difficult without knowing underlying structural volumes. In addition, understanding how persons with a schizophrenia spectrum disorder process information may be invaluable for family members coping with these devastating conditions.

Acknowledgments

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TABLE 1

Morphological Studies of SPD

Study	Subjects	Regions examined/measures	Findings	Comments
Schulsinger et al.[84]	33 offspring of mothers with SZ (11 with borderline SZ [probably SPD], 8 with SZ, 14 mentally healthy)	Lateral ventricle, third ventricle, VBR	Subjects with SZ had largest ventricles, followed by mentally healthy subjects; those with borderline SZ had the smallest	CT study; each measurement performed on 1 slice. Subjects with borderline SZ had fewer obstetrical complications than did those with SZ.
Cannon et al.[57]	34 offspring of mothers with SZ (12 with SPD, 7 with SZ, 15 unaffected)	Maximum width of sylvian fissure, width of anterior interhemi spheric fissure, mean width of 3 broadest cortical sulci, width of third ventricle, area of lateral ventricle, VBR, qualitative assessment of cerebellar vermis	Enlarged third ventricles correlated with lower heart rate 18 y previously	CT study; each measurement performed on 1 slice, sometimes using calipers. Sample overlaps with Schulsinger et al.[84] Authors also measured heart rate on enrollment in the study, 18 y previously. The 3 groups were not compared on CT measures.
Raine et al.[75]	17 with schizotypal features, but not SPD	Prefrontal cortex, temporal lobe	High scores on schizotypy scales correlated with reduced left prefrontal area and with high left and right prefrontal:temporal lobe area ratios	MRI study, 0.15-T magnet; 12 slices, 10 mm thick, with single slices used for measures of prefrontal and temporal cortex
Cannon et al.[57]	126 offspring of mothers with SZ (31 with SPD, 17 with SZ, 33 with another diagnosis, 45 with no diagnosis) and 77 offspring of NC mothers (1 with SZ, 4 with SPD, 26 with another diagnosis, 46 with no diagnosis)	Ventricles and sulci, VBR, sulcus:brain ratio, temporal and frontal fissures, lateral ventricles	Offspring of mothers with SZ who had SZ or SPD showed larger sulci than did any other group; offspring of mothers with SZ who had SZ had larger ventricles than did any other group	CT study; 13 slices, 8 mm thick. The sample overlaps in part with those of Schulsinger et al.[84] and Cannon et al.[56]
Hendren et al.[78]	25 children aged 8–12 y (12 with symptoms of SPD or early-onset SZ, 13 NCs	Amygdala, hippocampus, part of temporal cortex (slices on which amygdala and hippocampus could be visualized), corpus callosum area, cerebellum area, frontal lobe area (on midsagittal slice), lateral ventricle, third ventricle, temporal horn	Children with symptoms of SPD or SZ had reduced amygdala and temporal cortex volumes, callosal area	MRI study, 1.5-T magnet; area measures were performed on 1 slice. MRS data were also reported for 9 subjects and 8 controls. Poor complex verbal memory was seen in children with symptoms of SPD or SZ.
Siever et al.[74]	36 with SPD, 23 with other personality disorders, 133 with SZ, 42 NCs	VBR, frontal and posterior horns of lateral ventricle, third ventricle	VBRs of subjects with SPD were higher than those of subjects with other personality disorders and were intermediate between (but not significantly different from) VBRs of NCs and those of subjects with SZ	CT study (2 different scanners used); slices 0.8–1.0 cm thick, depending on scanner. Some of the subjects with SPD had been exposed to neuroleptics.
Shihabuddin et al.[82]	11 individuals from a single pedigree (2 with SPD, 3 with SZ, 6 unaffected)	Lateral ventricles, VBR, anterior horn, temporal horn, measure of sulcal CSF by brain region	Affected subjects plus 1 unaffected subject (all of whom carried a genetic marker for schizophrenia) had larger ventricles, a higher VBR, and larger CSF volumes in frontal and parietal regions than did the 5 subjects not carrying the marker	CT study; slices 8 mm thick. Data for subjects with SPD were not analyzed separately.

Study	Subjects	Regions examined/measures	Findings	Comments
Buchsbaum et al.[50]	12 with SPD, 11 with SZ, 23 NCs	Lateral ventricles, anterior horn, temporal horn	Left anterior and temporal horn volumes in subjects with SPD were between those of NCs and those of subjects with SZ, differing significantly from the latter	MRI study, 1.5-T magnet;[*] slices 1.2 mm thick
Kwon et al.[53]	16 with SPD, 5 with subthreshold SPD,[†] 15 with chronic SZ, 15 with first- episode SZ, 16 with first-episode psychotic affective disorder, 46 NCs	Presence of large cavum septi pellucidi	A large cavum septi pellucidi was more common in subjects with SZ than in NCs (found in 27.3% of subjects with SPD, 35% of those with SZ, 25% of those with psychotic affective disorder, and 13% of NCs)	MRI study, 1.5-T magnet. Appearance of cavum was evaluated on 1.5-mm slices.
Silverman et al.[83]	11 with SPD (at least 4 criteria),[‡] 42 with SZ, 6 with SCA, 56 unaffected relatives, 22 NCs	VBR	No difference was seen between subjects with SPD and those with SZ; subjects with SZ and SPD had higher VBRs than did their unaffected relatives	CT study; slices 8.0 mm thick. One slice used for comparison.
Dickey et al.[54]	16 with SPD, 5 with subthreshold SPD,[†] 14 NCs	Superior temporal gyrus, amygdala, hippocampus, parahippocampus	Subjects with SPD showed reduced superior temporal gyrus volume and differences in parahippocampal asymmetry compared with NCs	MRI study; 1.5-T magnet; slices 1.5 mm thick. Sample overlaps with that of Kwon et al.[53]
Hazlett et al[51]	13 with SPD, 27 with SZ, 32 NCs	Thalamic volume, thalamus:brain ratio	No differences were seen in thalamic volume; shape analysis suggested fewer pixels in the right mediodorsal nucleus in subjects with SPD than in NCs, and fewer pixels in the left anterior regions in subjects with SZ than in NCs	MRI study, 1.5-T magnet;[‡] slices 1.2 mm thick. Study also included a PET component, which showed no difference in thalamic metabolism between subjects with SPD and NCs (although the subjects with SZ had lower bilateral metabolism in the mediodorsal nucleus of the thalamus than did subjects with SPD or NCs).
Warwick et al.[77]	32 with sex chromosome aneuploidies (11 with 47 XXX, 10 with 47 XYY, 10 with 47 XXY), 38 NCs[§]	Whole brain, R and L prefrontal lobes, R and L temporal lobes, R and L lentiform nuclei, R and L caudate nuclei, R and L amygdalohippocampal complex, lateral ventricles, third and fourth ventricles	SIS scores for introversion, magical thinking, and impulsivity did not correlate with whole brain volumes for the XXX group: females with XXX had smaller whole brains than did female NCs, males with XXY had smaller whole brains and larger lateral ventricles than did male NCs.	MRI study, 1.0-T magnet. Study based on reports of increased incidence of schizotypal traits in persons with sex chromosome aneuploidies. Data for subjects scoring high on the SIS were not analyzed separately.
Dickey et al.[55]	16 with SPD, 14 NCs	Lateral ventricles, temporal horn, total CSF, cortical gray matter, total gray matter, white matter	Subjects with SPD had greater CSF volumes (but not ventricular volumes) than did NCs; a trend was seen toward reduced cortical gray	MRI study, 1.5-T magnet; slices 1.5 mm thick. Sample overlaps with those of Kwon et al.[53] and Dickey et al.[54]

Study	Subjects	Regions examined/measures	Findings	Comments
			matter volumes in subjects with SPD compared with NCs	
Downhill et al.[49]	13 with SPD, 27 with SZ, 30 NCs	Shape and size of corpus callosum; volume of lateral ventricles and anterior and temporal horns	The genu was larger in subjects with SPD than in those with SZ or NCs; a region of the callosum just posterior to the genu was smaller in subjects with SPD than in those with SZ or NCs; the genu and splenium together were smaller in subjects with SZ than in NCs; no correlation was seen between corpus and ventricular measures in subjects with SPD	MRI study, 1.5-T magnet;[‡] slices 1.2 mm thick. Sample overlaps, in part, with that of Buchsbaum et al. [50]
Kurokawa et al.[81]	4 with SPD, 4 with SZ, 7 with OCD, 1 with BDD, 14 NCs	Lateral ventricles, inferior horn, third ventricle, VBR on 3 slices	The inferior horn was larger and the VBR was higher in subjects with SPD or SZ than in those with OCD or NCs; the third ventricle was larger and the VBR was higher in subjects with SPD/SZ than in those with OCD	MRI study, 1.5-T magnet; slices 1.0 mm thick; measurements were performed on only 3 slices. All 4 subjects with SPD were treated with neuroleptics (type unspecified), and 2 were treated with clomipramine. Data for subjects with SPD were not analyzed separately.
Byne et al.[52]	12 with SPD, 12 with SZ, 12 NCs	Thalamus, pulvinar, mediodorsal nucleus of thalamus	No differences were seen in the thalamus; pulvinar volumes and combined pulvinar/mediodorsal nucleus volumes were smaller in subjects with SPD or SZ than in NCs; the mediodorsal nucleus was smaller in subjects with SZ than in NCs	MRI study; 1.5-T magnet; slices 1.2 mm thick. Subsample of Hazlett et al.[51]

BDD, body dysmorphic disorder; *CSF*, cerebrospinal fluid; *CT*, computerized tomography; *MRI*, magnetic resonance imaging; *MRS*, magnetic resonance spectroscopy; *NC*, normal control; *NOS*, not otherwise specified; *OCD*, obsessive-compulsive disorder; *PD*, personality disorder; *PET*, positron emission tomography; *SIS*, Structured Interview for Schizotypy; *SPD*, schizotypal personality disorder; *SZ*, schizophrenia; *SZA*, schizoaffective disorder; *VBR*, ventricle:brain ratio.

[*] GE Signa 5X reported; we assume this was a 1.5-T system.

[†] Subjects met either three or four of the nine criteria for diagnosis.

[‡] Subjects with SPD and those who met four out of nine criteria were analyzed together. How many subjects actually met criteria for SPD is unclear.

[§] An unclear number of subjects scored high on the SIS.

TABLE 2

Comparison of Morphological Abnormalities in SPD with Those in First-Episode Schizophrenia and First-Episode Psychotic Affective Disorder

Abnormality	SPD	FE SZ	FE AFF
Sulcal CSF increase	Yes	Yes	No
Cortical gray matter decrease	Trend	Left	No
Left STG gray matter decrease	Yes	Yes	No
Posterior STG subdivisions decrease			
Heschl's gyrus	Yes	Yes	No
Planum temporale	No	Yes	No
Medial temporal lobe subdivisions decrease			
Amygdala	No	Yes	Yes
Hippocampus	No	Yes	Yes
Parahippocampus	Asymmetry	Yes	Yes
Large cavum septi pellucidi	Yes	Yes	Yes

AFF, psychotic affective disorder; *CSF*, cerebrospinal fluid; *FE*, first episode; *SPD*, schizotypal personality disorder; *STG*, superior temporal gyrus; *SZ*, schizophrenia.