New Perspectives on Schizotypal Personality Disorder

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Schizotypal personality disorder is the prototype of the schizophrenia-related personality disorders and has been demonstrated to have phenomenologic, biologic, treatment, and outcome characteristics similar to those of schizophrenic patients. These studies suggest that patients with schizotypal personality disorder, like schizophrenic patients, show cognitive impairment, but the impairment is more focal and involves primarily working memory, verbal learning, and sustained attention rather than generalized intellectual deficits. Schizotypal patients, like schizophrenic patients show reductions in temporal lobe volume, but seem to be spared the frontal volume reductions found in some studies of schizophrenic patients and in our laboratory. Better frontal "buffering" may prevent the more severe cognitive and social deterioration associated with schizophrenia. Furthermore, schizotypal patients appear to show less susceptibility to psychotic symptoms, in part perhaps because of better buffered subcortical dopaminergic activity as suggested by recent data from a SPECT/amphetamine paradigm, glucose metabolic study, and structural studies of basal ganglia. These findings are discussed in terms of a model of schizotypal personality disorder where schizotypal patients have better capacity for compensatory buffering in lateral and subcortical brain regions, protecting them from the more severe symptoms of chronic schizophrenia.

Introduction

Patients with schizotypal personality disorder (SPD) share with schizophrenic patients a common phenomenology including the social deficit symptoms, a similar but less pervasive cognitive impairment, neuroimaging and neurochemical evidence of brain dysfunction, and common genetic substrates. However, patients with SPD are spared the chronic psychosis of schizophrenia. In order to better understand the common genetic and biologic substrates of the schizophrenia spectrum disorders, as well as the differences between schizophrenic and schizotypal patients, and to identify those factors that protect the schizotypal patient from chronic psychosis, the investigation of schizotypal patients becomes of critical importance. In this article we summarize recent findings regarding the substrates of schizotypal personality disorder and show how these findings may contribute to our understanding of risk/vulnerability factors and protective factors in the schizophrenia spectrum.

Phenomenology

The criteria for schizotypal personality disorder represent what might be considered attenuated symptoms of schizophrenia itself. They include the "positive" psychotic-like symptoms of magical thinking, perceptual distortions, and referential ideas; the "negative" or social deficit-like symptoms of social isolation, constricted affect, and social anxiety; and the "disorganized symptoms" that include eccentric appearance, and odd speech [1]. Other factor structures for SPD have been found including that of psychotic-like, deficit-like, and paranoid symptoms [2]. One twin study found that positive or psychotic-like symptoms were independently heritable from the negative or deficit symptoms [3]. These considerations raise the possibility that the psychotic-like symptoms and social deficit symptoms as well as possibly the disorganized symptoms of SPD may have different biologic substrates. This has also been suggested in some models of the biologic substrates of positive and negative symptoms of schizophrenia. This possibility will be addressed as findings are reviewed in each domain.

Attentional Function

Patients with SPD show impairment of their smooth pursuit eye movements. This impairment is characterized by reduced gain, excessive saccades, and greater time spent off the target [4,5]. Patients with SPD perform more poorly on tasks requiring sustained attention, such as the Continuous Performance Task (CPT), especially under conditions where perceptual or cognitive demands are greater. Thus, patients with SPD do not differ from normal controls or other personality disorder patients on the CPT with normal stimuli, but do show impaired performance when the stimuli are degraded and thus more difficult to detect [6]. In an identical pairs version of the CPT (CPT-IP) which also has a higher processing load, SPD patients

perform worse than other personality disorder patients or normal controls [7]. Backward masking performance has also differentiated patients with SPD from controls in some studies [8,9] but not others [6].

Patients with SPD show deficits in tests of executive function sensitive to frontal lobe damage. For example, a number of studies have shown that patients with SPD perform more poorly on the Wisconsin Card Sort Test (WCST) than do controls [10,11]. The WCST depends on a variety of executive functions including working memory, abstraction, and set shifting. A more specific test of visuospatial working memory is the Dot test. This is a test that assesses an individual's capacity to recall the position of a dot in a circular or semi-circular array. This test has revealed differences between SPD patients and both normal and other personality disorder control groups. Patients with SPD at a variety of intervals from presentation of stimulus show poor recollection of the dot's position, although they do not differ from controls in their immediate recall of the position of the dot [12]. SPD patients also show deficits in verbal learning as measured by the California Verbal Learning Test. In one study, it appeared that patients showed deficits in somatic cueing and their rate of learning was poorer than controls [13], and in another study from our center patients showed impaired recall both at the first and the last presentation of the words [14]. SPD patients also show reduced performance on the Stroop Color Word Interference Test and verbal fluency tasks [11]. Recent studies demonstrate language dysfunction in SPD patients, with an abnormal electrophysiological correlate of this dysfunction [15]. However, patients with SPD do not have generalized reductions in intelligence [11], suggesting that these patients exhibit selected deficits in working memory, verbal learning, and attention.

Structural Abnormalities

Patients with SPD, like schizophrenic patients, show abnormalities in brain structure as detected by computed tomography scan or magnetic resonance imaging (MRI). Ventricular enlargement has been observed in samples of clinically identified SPD patients [16] as well as relatives of schizophrenic patients [17] and schizotypal volunteers. Reports of enlarged ventricular space have been confirmed using more precise MRI measurements [18]. Furthermore, abnormalities such as reduced volume in temporal lobe and hippocampus have been found in schizotypal patients, as they have in schizophrenic patients [19,20]. MRI studies have also shown abnormalities of the cavum septum pellucidum in SPD; these abnormalities were intermediate between schizophrenic and normal subjects, suggesting that alterations in midline structures during the course of neurodevelopment may play a role in the pathogenesis of the schizophrenia spectrum [21]. Frontal lobe volume has been reported to be inversely associated with tests of executive function in normal volunteers with schizotypal symptoms [21] and in clinically selected schizotypal patients [23]. However frontal lobe volume does not appear to be reduced in SPD patients compared to controls, in contrast to reductions reported in schizophrenic patients [24]. Preliminary analyses from our center suggest that while tests of executive or frontal function as well as the social deficit symptoms of SPD correlate inversely with the volume of frontal lobes, volume of the superior temporal gyrus is inversely associated with performance on verbal learning tasks and with the disorganization symptoms of SPD. Interestingly, psychotic-like symptoms were associated with increases in putamen volume of the basal ganglia. These results are consistent with data from schizophrenic patients suggesting inverse relationships between temporal volume and indices of thought disorder and verbal learning as well as between frontal volumes and performance on executive function neuropsychologic tasks.

Functional Imaging

Functional imaging studies have been performed on SPD patients and controls in our center, to test the possibility that SPD patients are able to utilize brain regions not normally recruited for specific cognitive functions, in order to compensate for deficits or dysfunction in the primary region associated with that cognitive function. An initial study using regional cerebral blood flow imaging to visualize brain blood flow during performance of the Wisconsin Card Sort Test (WCST) was performed. Normal control subjects showed activation in the precentral frontal cortex while performing the test, whereas SPD patients showed lesser activation in this area and greater activation in other prefrontal regions such as middle frontal gyrus, suggesting compensatory activation in related regions. There was a significant hemisphere by region interaction suggesting altered lateralization [25]. In another preliminary study, SPD patients, normal controls, and schizophrenic patients were evaluated during their performance in a verbal learning task with fluorodeoxyglucose positron emission tomography (FDG PET) scanning. The SPD patients showed abnormalities in temporal activation as did schizophrenic patients compared with controls. Schizophrenic patients showed reduced frontal activation compared to normal controls, whereas SPD patients showed lesser reductions and increased “compensatory” activation of other frontal regions compared to schizophrenic patients and normal controls.

Neurochemistry

Although indices of dopamine activity have not generally distinguished patients with schizophrenia from control populations, some suggestions of increased cerebrospinal fluid (CSF) homovanillic acid (HVA) have been found in

paranoid schizophrenia, whereas reductions in plasma or CSF HVA have been found in chronic deficit-like schizophrenic patients [26]. In SPD patients, initial studies suggested increases in plasma HVA in clinically selected SPD patients compared to other personality disorder patients or controls, and these increases were associated with a number of psychotic-like symptoms [23]. Indeed, when psychotic-like symptoms were covaried these differences were no longer apparent. Similar results have been found using CSF HVA, with increases in SPD patients associated with increased psychotic-like symptoms. In relatives of schizophrenic patients with SPD, the psychotic-like symptoms were also associated with increases in plasma HVA; however, the net plasma HVA concentrations were in fact lower in the SPD relatives than in relatives with no personality disorder or other nonschizotypal personality disorders [27]. These relatives seem to display primarily deficit-like symptoms and plasma HVA concentrations were inversely correlated with the deficit-like symptoms of this disorder, which appear to account for the SPD patients' lower mean values [27]. Some studies of schizotypal patients also suggest reduced concentrations of plasma HVA to be associated with poorer performance on cognitive tests [23]. Cumulatively, these studies raise the possibility that positive or psychotic-like symptoms are associated with increases in plasma HVA whereas deficit-like symptoms and cognitive impairment are associated with decreases in plasma HVA.

Pharmacologic Interventions

Several studies suggest that treatment with neuroleptic medication can reduce some of the symptoms of schizotypal personality disorder, particularly the psychotic-like symptoms and social anxiety associated with this disorder [28]. Studies with agents such as thiothixene [28], haloperidol [29], and risperidone [30] may be helpful in alleviating the symptomatic distress of schizotypal personality disorder.

However, it would be desirable to find pharmacologic interventions that would enhance the functioning of schizotypal patients by reducing their deficit-like symptoms and enhancing cognitive performance. In one study at our center, SPD patients administered 30 mg of amphetamine in placebo-controlled fashion showed an improvement in their WCST performance, with the worst performers on placebo showing the most improvement [31]. In another overlapping series of patients, the same amphetamine dose resulted in a reduction in position error on the working memory test, the Dot test, in schizotypal patients, whereas no such difference was observed in other personality-disordered patients [32]. The 30 mg amphetamine dose compared with placebo also resulted in improvement on a verbal learning test and in the performance on the CPT in the SPD patients but not other personality-disordered controls [32]. Amphetamine acts largely through D1 receptors in frontal cortex. D1 receptors are known to modulate the performance of visuospatial working memory in primates [33]. Amphetamine may also serve to enhance cortical striatal dopaminergic transmission and may be important for performance on the CPT. Dopaminergic modulation may also enhance verbal learning through subcortical frontal and subcortical temporal connections. In our pilot study, amphetamine showed a clear enhancement of visuospatial delayed memory which was greater in schizotypal than in other personality-disordered controls, and verbal learning and CPT accuracy increased also. These results suggest that dopaminergic enhancement may indeed be of benefit in reducing cognitive impairment in schizotypal patients.

Interestingly, there were no changes in positive schizotypal symptoms following amphetamine, in contrast to studies of schizophrenic patients in which half the patients may show worsening of psychotic-like symptoms. However, negative schizotypal symptoms did improve. This consideration raises the possibility that schizotypal patients may be better "buffered" against subcortical dopaminergic overactivity associated with psychosis.

Schizotypal Personality Disorder as a Model for Understanding the Pathophysiology of the Schizophrenic Disorders

Because patients with SPD are not as likely to have been institutionalized, have received long-term neuroleptic medication, or have suffered the effects of chronic psychosis, their study is less confounded by these artifacts endemic to research of patients with chronic schizophrenia. Furthermore, because schizophrenia may be considered an end-stage disease that likely derives from multiple, interacting pathophysiologic processes, the study of the less severely impaired schizotypal patient may allow a disentangling or unraveling of these convergent pathophysiological strands to better isolate specific processes that confer vulnerability to the schizophrenia spectrum, but also to isolate factors that may be protective against chronic psychosis.

Along these lines, it is clear that patients with SPD often share the cognitive impairment, perhaps to an attenuated degree, observed in schizophrenia, and that they display the same kind of asocial behavior and detachment from others. Although schizotypal patients may exhibit psychotic-like symptoms like suspiciousness or mild referential ideation, they do not display the overt hallucinations or delusions that schizophrenic patients do. Even on provocation with the potentially psychotogenic agent amphetamine, SPD patients are remarkably well buffered from the emergence of psychosis. Thus, schizotypal patients may share with schizophrenic patients a common neurodevelopmentally based disorder of cortical organization and function, manifest as impairment in working and verbal memory and attention as well as in the social deficit symptoms, but may be less likely to show a

subcortical overactivity associated with psychosis that may be seen in classic schizophrenia.

Chronic schizophrenia appears to represent the final common pathway of a number of pathophysiologic processes impairing brain development. For example, evidence suggests that neonatal lesions in the temporal or hippocampal regions may result in frontal cortical dysfunction [34]. Coincident with this model, smaller volumes of hippocampal areas on MRI are associated with worse performance on the WCST, and are found in monozygotic twin pairs one of whom is schizophrenic [35]. Frontal cortical impairment can in turn result in upregulation of subcortical dopaminergic function [36–38]. Thus, deficits in cortical function, particularly in cortical dopaminergic pathways, may result in overactivity of dopaminergic pathways subcortically. Overactivity of subcortical dopamine systems has been associated with psychosis. Using a new brain imaging technique, amphetamine-induced dopamine release was assessed by the reduction in D2 receptor availability induced by an acute amphetamine challenge. Reduction in D2 receptor availability was measured using single photon emission computed tomography and a D2 radiotracer. This technique has shown a significantly greater reduction in D2 receptor availability in patients with schizophrenia than in normal controls. This displacement of dopamine is associated with increases in synaptic dopamine in patients with schizophrenia [39•,40]. Subcortical dopaminergic overactivity may also adversely affect cortical function. These propagating circuits of pathophysiology may be critically important in the development of the pervasive pathophysiology of schizophrenic disorders.

Thus, it becomes particularly important to identify what factors protect SPD patients from developing the severe, pervasive deficit symptoms and florid psychotic symptoms associated with chronic schizophrenia. In the face of temporal lobe or hippocampal dysfunction as a result of genetic or early environmental factors, SPD patients may not be as vulnerable to the same degree of frontal dysfunction, perhaps because of their capacity to recruit other related regions to compensate for dysfunctional areas, or because of greater frontal "reserves" (as suggested by the reduced frontal volumes in schizophrenic patients compared with SPD patients). Also, SPD patients may be less vulnerable to subcortical dopaminergic upregulation in the face of frontal cortical dopaminergic deficits and frontal dopaminergic underactivity. Thus, the cortical disorganization and dysfunction associated with the schizophrenia spectrum disorders does not necessarily translate into the chronic psychosis of the more severe schizophrenic disorders. Finally, a better buffered subcortical dysfunction may result in less propagation of this dysfunction to frontal and cortical regions. Thus, the schizotypal patient does not show the cascading pathophysiologies that might be expected in patients with chronic schizophrenia.

Conclusions

There are several lines of evidence suggesting that schizotypal personality disorder is phenomenologically, genetically, and biologically related to schizophrenia as part of a single continuum or spectrum of schizophrenia-related disorders. SPD patients have less severe symptoms and brain systems that may be better buffered so that brain abnormalities are less global and diffuse. In this regard, their study may provide a unique opportunity to dissociate pathophysiologic processes underlying the core deficit symptoms and cognitive impairment, on one hand, and the psychotic symptoms of the schizophrenia syndrome, on the other. In this article we have presented recent findings regarding biologic studies in patients with SPD, their phenomenology, cognitive function, structural brain abnormalities, neurochemistry as well as the neurotransmitter systems dysfunction in patients with this disorder that establish SPD as a schizophrenia spectrum disorder. We have outlined the factors that may place SPD patients in the same continuum as schizophrenic patients (*eg*, cognitive disorganization, temporal cortex volume reductions, *ie*, "risk factors") and the factors that may protect SPD patients from developing the chronic psychosis associated with schizophrenia (*eg*, reduced subcortical activation, *ie*, "protective factors"). Further work is necessary to better characterize these substrates.

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