

**The Pathophysiology of the Schizophrenic Disorders:
Perspective from the Spectrum
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Abstract

Objective: This overview focuses on neurobiologic abnormalities found in subjects with schizotypal personality disorder, the prototype of the schizophrenia spectrum disorders, and chronic schizophrenia in the context of common vulnerabilities shared by SPD and schizophrenia, as well as those factors that protect against the severe cognitive/social deficits and frank psychosis of chronic schizophrenia. A pathophysiologic model of the relationship between schizotypal personality disorder and schizophrenia is developed on the basis of this data.

Method: The authors provide a selective review of major findings regarding the pathophysiology of schizotypal personality disorder and integrate these results in conjunction with preclinical studies into a model of the pathophysiology of the spectrum.

Results: People with schizotypal personality disorder share phenomenologic, genetic, and cognitive abnormalities with people with chronic schizophrenia. While temporal volume reductions appear to be common to both groups, there may be preservation of frontal lobe volume in SPD compared to schizophrenia. Findings to date regarding striatal volume, metabolic rate, and dopamine release in SPD subjects compared to chronic schizophrenic subjects are consistent with hypotheses of reduced striatal dopaminergic activity in SPD compared to schizophrenia.

Conclusions: Genetic/environmental factors that promote greater frontal capacity and reduced striatal dopaminergic reactivity might contribute to the sparing of people with SPD from the psychosis and the severe social and cognitive deterioration of chronic schizophrenia. Further research is required to more definitively test these hypotheses.

Introduction

It is generally acknowledged that schizophrenia has a multifactorial etiology with multiple susceptibility genes interacting with environmental insults to yield a range of phenotypes in the schizophrenia spectrum. The field has moved to parse the underlying etiologic components of schizophrenia using, for example, candidate gene, imaging, and cognitive science strategies that increasingly employ other populations than schizophrenia itself including sib/relatives of schizophrenic patients, healthy volunteers, subjects prodromal for schizophrenia, and schizophrenia-related personality disorders. The cross-sectional study of the naturalistic variability of the schizophrenia spectrum, including schizotypal personality disorder (SPD), offers one unique and understudied vantage point from which to understand the schizophrenic disorders. Indeed, a strategy of investigating the similarities and differences between chronic schizophrenia and milder spectrum disorders can facilitate the dissociation of those pathophysiologic mechanisms which are associated the core cognitive and social impairment of this spectrum of disorders from those associated with recurrent or chronic psychosis as well as with the more extreme cognitive and social deficits of chronic schizophrenia. In this overview, we present studies (summarized in the text and tables) using comparable research paradigms in subjects with chronic schizophrenia, which have been reviewed more extensively in other articles including metaanalyses but are summarized here, and in subjects with SPD, which while much more limited in number and sample size, serve to illustrate the potential power of this strategy, which has received only limited attention to date in the field. We focus in this overview on studies of subjects selected to meet DSM criteria for schizotypal personality disorders rather than studies of relatives of schizophrenia probands or college student volunteers selected on the basis of self-report scales of schizotypy. While we acknowledge the limitations of data available from SPD subjects, we propose a theoretical model generating testable hypotheses to stimulate further investigation using this paradigm.

People with schizotypal personality disorder share common phenomenologic, genetic, biologic, outcome, and treatment response characteristics with more severely ill chronic schizophrenic patients. However, at the same time, they are freer from the multiple artifacts that potentially confound research in schizophrenia including the effects of long-term and usually ongoing medication treatment, multiple hospitalizations or institutionalization, and prolonged functional impairment secondary to chronic psychosis and social deterioration. SPD patients share with schizophrenic patients their persistent asociality and cognitive impairment, albeit to a milder degree, presumably emerging from common spectrum-related risk factors both genetic and

environmental (1). Yet, while chronic schizophrenia as the “end-stage” disease of the schizophrenic continuum or spectrum is characterized by severe, generalized deterioration across a variety of domains including cognitive and social function, the deficits of SPD patients are more circumscribed and selective. An identification of those factors, such as altered brain regional structure and function, associated with the severe deficits and cognitive deterioration of chronic schizophrenia in contrast to the milder impairment of schizotypal personality disorder might enhance the possibilities of preventing or ameliorating the social/cognitive dysfunction of schizophrenia. An identification of those factors that mitigate against the emergence of psychosis and serious cognitive deterioration in SPD patients (or alternatively, extra liability factors in schizophrenic patients that confer a greater susceptibility to psychosis and cognitive impairment) is critical in formulating interventions to reduce the morbidity of psychotic exacerbations in schizophrenic patients. Thus, we posit that there are several partially separable but interactive pathophysiologic processes in schizophrenia and that the study of SPD subjects offers a unique opportunity to tease apart these processes.

In this paper, we selectively review the phenomenologic, genetic, psychophysiological, cognitive, imaging and neurochemical studies that might inform the hypotheses of the pathophysiology of the schizophrenia spectrum followed by the outlines of a proposed physiologic model of the schizophrenia spectrum that incorporates these findings. Such a model generates research strategies, questions that can help realize a more specific understanding of the neurodevelopmental, cellular, and ultimately, molecular basis of the schizophrenic disorders as well as having implications for genetic, prodrome, and treatment studies.

Phenomenology

Schizotypal personality disorder, like schizophrenia, is characterized by “positive” or psychotic-like symptoms and “negative” or deficit-like symptoms. Psychotic-like symptoms include ideas of reference, cognitive/perceptual distortions, and magical thinking. In factor analyses of schizotypal subjects, two other factors emerge from the more broadly defined deficit-like symptoms: social deficit or “interpersonal” symptoms and usually a third factor - either cognitive disorganization or paranoid symptoms (2, 3). These dimensions may have partially distinct underlying pathophysiologies providing an opportunity to dissect them from each other in studies of SPD.

Genetics

While genetic studies, both twin and adoptive, have clearly identified a genetic basis for the schizophrenia spectrum disorders (4), the nature of these genetic factors and their range of phenotypic expression remains unclear. The less than complete concordance of schizophrenia in identical twins also suggest that other non-genetic factors must influence the expression of this disorder. Many co-twins of schizophrenic probands show attenuated schizophrenia-like traits, although there is considerable variability in their expression. In general, family and twin studies suggest that the deficit-like symptoms of schizotypal personality disorders or other schizophrenia-related disorders may be most characteristic of schizotypal individuals with a genetic relationship to schizophrenia (5, 6).

Both family and adoptive studies (7-10) suggest an increased prevalence of schizotypal personality disorder in relatives of schizophrenic patients compared to control groups. While an increased prevalence of SPD is found in relatives of SPD probands compared to controls, an increased prevalence of chronic schizophrenic in relatives of SPD is not found as consistently as in studies of schizophrenia probands (11-15). This pattern is consistent with the hypothesis that susceptibility genes for psychosis are less prevalent in families of SPD probands than those of schizophrenic probands.

There is emerging evidence that the psychotic-like and deficit-like symptoms might have independent heritability in normal and schizophrenia spectrum subjects. Both twin studies of normal volunteers and family studies of schizophrenic patients suggest that there are two heritable factors in schizotypy: one related to the “positive” symptoms and the other related to the “negative” symptoms and cognitive impairment of the spectrum (16, 17). The prevalence of both the schizophrenia related personality disorders and psychosis are higher in relatives of schizophrenic probands than in the relatives of affective disorder probands, but schizophrenia spectrum personality disorders, characterized by eccentricity and social deficits, and psychotic disorders do not necessarily occur in the same relatives (4, 5, 18). These data are consistent with partially independent transmission of one set of genetic factors common to the spectrum that are largely manifest in social and cognitive deficits (“spectrum phenotype”) and other distinct genetic factors related to psychosis (“psychotic phenotype”).

Table 1: Psychophysiology †

	Chronic Schizophrenia		Schizotypal Personality Disorder	
	Character of Abnormality	Effect Size	Character of Abnormality††	Effect Size*
Eye Movement Impairment	Inability to follow target smoothly	Large(28,31,47)	Inability to follow target smoothly	Small(29)
Anti-Saccade	Abnormal: gaze initially directed towards target instead of away from target	Large(28,47)	Abnormal: gaze initially directed towards target instead of away from target	Large(29)
Backward Masking	Impaired: demonstrate masking effects at an interstimulus interval that is easy for normal controls	Medium(47)	Impaired: demonstrate masking effects at an interstimulus interval that is easy for normal controls	Medium(109)
P ₅₀ Suppression	P ₅₀ suppression deficit	Large(19,47)	P ₅₀ suppression deficit	Large(20)
P ₃₀₀ Event-related Potential	Reduced amplitude of P ₃₀₀ wave	Medium-large(47)	Reduced amplitude of P ₃₀₀ wave	Small-medium(26,27)
N ₄₀₀ Event-related Potential	Reduced in amplitude	Large (auditory and visual)(24,25)	Reduced in amplitude	Large (auditory and visual)(25)
Prepulse Inhibition	Reduced gating/inhibition	Medium-large(22,47)	Reduced gating/inhibition	Large(23)
Latent Inhibition (LI)	LI reduced with higher levels of psychosis (positive symptoms)	Variable(37,38)	High schizotypy male subjects have LI, high schizotypy female subjects fail to have LI	Variable(39)
Negative Priming	Reduced (spatial): related to positive symptoms	Large(41,42)	High schizotypy subjects have less negative priming than low schizotypy subjects	Variable(40,42)

† Partially adapted from (47) (with permission from the authors and publisher)

†† Compared to normal controls unless otherwise specified

* SPD effect sizes based upon a small number of studies (generally 1-3), so confidence interval is limited

Effect Size scale:

.2=small

.5=medium

.8=large

>1.4= large

>2= large

Variable: inconsistent results across studies

Psychophysiology

Patients with schizotypal personality disorder share a number of psychophysiological abnormalities found in chronic schizophrenia (see Table 1 for psychophysiological correlates or intermediate phenotypes for schizophrenia and SPD). These include a failure of P50 suppression or the capacity to “gate” or appropriately modulate/inhibit sensory input that may result in sensory overload and cognitive disorganization; deficits in pre-pulse inhibition, the capacity to inhibit the startle response with a weak pre-stimulus, which may impair appropriate modulation of responsiveness to the environment; impairment of smooth pursuit eye movements, which enable the fovea to maintain its focus on a smoothly moving target, reflecting involuntary attention; errors in antisaccade tasks, which test saccadic inhibition; poor performance on a backward masking task that assesses early visual processing; reduced P300 evoked potentials, which measure auditory attention; and performance on the Continuous Performance Task (CPT), a sustained attentional task.

P50 suppression abnormalities are heritable, have also been identified in SPD patients as well as clinically unaffected relatives of schizophrenic subjects, and are modulated by nicotinic receptors in hippocampus (19, 20). Indeed, using the reduced P50 evoked potential as an endophenotype in a linkage study of families of schizophrenic subjects resulted in the demonstration of linkage of this phenotype to a variant of the alpha-7 nicotine receptor gene (21). Pre-pulse inhibition in a blink startle paradigm has also been identified in schizophrenic patients, schizotypal individuals, and relatives of schizophrenic patients and is modulated by cortico-striato-pallido-thalamic circuitry (22, 23). Reduced N400 evoked potentials, critically modulated by ventral temporal regions, are reduced throughout the spectrum and may reflect a failure of recurrent inhibition (24, 25). Evoked potential abnormalities, particularly reduced P300 amplitude, have been reported in schizotypal subjects and have been associated with smaller left posterior superior temporal gyrus volume in schizophrenic patients (26, 27).

Schizophrenic patients not only demonstrate qualitative and quantitative impairment in smooth pursuit tracking but also perform less accurately in

antisaccade and in motion detection tasks (28, 29). Smooth pursuit eye movements are mediated by frontal and temporal cortex, as well as brain stem, while motion detection is mediated by inferior temporal cortex (30). SPD subjects show impairment in smooth pursuit tracking measured qualitatively and by indices such as tracking gain and saccadic intrusions just as do schizophrenic patients.

Table 2: Cognitive Functioning

	Chronic Schizophrenia		Schizotypal Personality Disorder	
	Character of Abnormality	Effect Size	Character of Abnormality	Effect Size *
Working Memory Visuospatial (DOT, WMSV-R immediate)	Impaired (especially with longer delays)	Large- large(34)	Impaired (especially with longer delays)	Medium-large(44,50)
Working Memory Auditory (PASAT)	Impaired (failure to respond and increased incorrect additions)	Large(34,48)	Impaired (failure to respond and increased incorrect additions)	Large(44)
Episodic Memory (WMSV-R delayed)	Impaired	Large(34)	Impaired	Medium-large(44)
Verbal Learning (CVLT)	Decreased number of free recalled words	Large(34)	Decreased number of free recalled words	Variable(44,51)
Attention Continuous Performance Task (CPT)	Increased errors of omission and commission	Large(34,35)	Increased errors of omission and commission	Medium(33)
Executive Function WCST	Impaired (increased number and percent of perseverative errors)	Large(34,47,110)	Impaired (increased number and percent of perseverative errors)	Medium(45)
Trail B	Impaired	Large-large(34,111)	Impaired	Medium(44,45)
General IQ WAIS Vocabulary	Impaired	Large (112)	No difference to impaired	Variable(44,45,51)
WAIS Block	Impaired	Large(34)	Impaired	Medium(44,45,51)

* SPD effect sizes based upon a small number of studies (generally 1-3), so confidence interval is limited

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>1.4= large

>2= large

Variable: inconsistent results across studies

These abnormalities are particularly correlated with the social deficits and interpersonal isolation of these patients (31). Schizotypal subjects, whether identified in samples of clinical, volunteer, or relatives of schizophrenic patients, also show deficits in d-prime, a measure of accuracy in performance, on the Continuous Performance Task (CPT), an attentional task that depends on fronto-striatal circuitry (32-35). Interestingly, schizotypal individuals perform relatively normally under low processing demand conditions such as non-degraded stimulus presentation, but perform more poorly than normal controls and other personality disorder comparison groups when stimuli were degraded or a more challenging identical pair CPT paradigm or a dual task CPT was utilized (33, 36). Other psychophysiologic/information processing abnormalities shared between SPD and schizophrenic subjects include latent inhibition (37-39), negative priming (40-42), and interference (43).

Some of these abnormalities such as those of P50 suppression, pre-pulse inhibition, eye movement abnormalities, and CPT performance are quite stable in normal subjects, persist in schizophrenic patients in remission from psychosis, and appear to be heritable, representing promising endophenotypes for genetic studies. They likely thus represent manifestations of genetic factors that span the schizophrenia spectrum. They have been associated with altered cortical circuitry particularly involving temporal and hippocampal regions that have been implicated in the core symptomatology, i.e., the cognitive and social deficits, of the spectrum. They particularly involve modulation of attention and inhibition of sensory input and motor output. To the extent they are shared between SPD and schizophrenic subjects, they are less likely to reveal those specific liability factors towards or mitigating factors against psychosis.

Cognitive Function

Schizotypal patients display selective deficits in cognitive processing similar to those observed in schizophrenic patients (44-46) (see Table 2 reflecting domains of cognitive performance impaired in schizophrenia where data is available for SPD subjects as well). While overall IQ seems to be preserved in SPD patients, schizotypal individuals evidence deficits in working memory and verbal learning as well as attentional deficits. Initial studies using a broad survey of cognitive tasks suggested impaired performance on the Wisconsin Card Sort (WCST) (45-47) in schizotypal patients as well as schizotypal relatives of schizophrenic patients. Schizotypal individuals also demonstrated less accurate responses on the Stroop Color-Word Interference Test and on the Trails B Test (44, 45) as well as other tests of executive function and abstraction (46). These data suggest deficits in executive function that are often compatible with prefrontal cortical impairment.

It has been suggested that impairment of these executive function tasks may, in large part be a function of impaired working memory (34, 44, 48, 49). While the WCST involves a component of spatial working memory, more direct tests of visuospatial working memory involving computerized or paper and pencil paradigms have demonstrated working memory impairment without visual processing defects in schizotypal subjects (50, 51) and relatives of schizophrenic patients (52).

Table 3: Structural Imaging

	Chronic Schizophrenia		Schizotypal Personality Disorder	
	Character of Abnormality	Effect Size	Character of Abnormality	Effect Size *
Whole Brain	No difference	No difference(75)	N/A	N/A
BRAIN REGION:				
CORTEX				
Frontal	Reduced in some	Small –medium(60,61,113)	No difference	N/A
Temporal	Gray matter volume reduced	Variable: Small – large(58,60,61)	Gray matter volume reduced	Large(62)
Whole				
Superior Temporal Gyrus	Gray matter volume reduced	Variable: Small – large(59-61)	Gray matter volume reduced	Variable: Medium - large(62,63)
Medial (Hippocampus and Amygdala)	Reduced in most studies	Small – medium(61)	No difference	N/A(63)
Planum Temporale	Reduced (left)	Large(114)	No difference	N/A(63)
Heschl's Gyrus	Reduced (left)	Medium(114)	Reduced (left)	Medium-large(64)
Anterior Cingulate Gyrus	Lack of normal asymmetry (reduced right gray matter)	Medium (left) – large (right)(116)	Females lack normal asymmetry (reduced right gray matter)	Small (left) – medium (right)(115)
Parietal	Reduced (greatest on left)	Small-medium(58,117,118)	No data (parietal atrophy in one study of relatives with SPD and schizophrenia associated with a linkage marker)	N/A
Occipital	Reduced (greatest on left)	Medium(58,60,117)	No data	N/A
STRIATUM				
Putamen	Increased	Small-medium(60)	Reduced	Small(76)
Caudate Nucleus	Increased	Large(75)	No difference-reduced	Large(77)
THALAMUS	Normal-slightly reduced	Small – medium(60,72,73)	No difference	N/A(72)
MDN	Reduced	Medium(60,72,73)	No difference	N/A(72)
Pulvinar	Reduced	Medium(60,72,73)	Reduced	Medium(72)
CEREBELLUM	No difference'	No difference(75)	No data	N/A
CORPUS CALLOSUM	Reduced and downward bowing, reduction in anterior of genu, and posterior of splenium	Total volume difference not significant(119)	Downward bowing, genu larger, smaller posterior than in normal controls	Total volume difference not significant(119)
CAVUM SEPTI PELLUCIDUM (CSP)	Increased, mostly in males	20.7% had large CSP (higher incidence than in normal controls), 35% show abnormal CSP***(58,120)	<i>Slightly increased</i>	27.3% show abnormal CSP versus 13% in normal controls(120,121)
CSF SPACE				
Left anterior horn	Increased (most prominent in temporal and frontal area)	Medium(117)	Increased	Small(55)
Left temporal horn	Increased	Medium –large(60)	Increased	Medium(55)
Lateral Ventricle	Enlarged, left>right asymmetry	Medium – large, large(60,75)	No difference	N/A
Third Ventricle	Enlarged	Medium - large(60,75)	No difference	N/A
Fourth Ventricles	No difference	N/A(58,60)	No difference	N/A

* SPD effect sizes based upon a small number of studies (generally 1-3), so confidence interval is limited

** Meta-analysis of several studies indicating percentage of subjects demonstrating abnormality

Effect Size scale:

.2=small

.5=medium

.8=large

>1.4=large

>2=large

Variable: inconsistent results across studies

Verbal learning and episodic memory deficits, reflected in initial word list learning and multi-trial memory learning, have also been reported in schizotypal individuals (34, 44, 46, 51, 53). Schizotypal individuals, on the other hand, appear to show no deficits in perceptual processing tasks such as the Benton Line Orientation, motor capabilities such as the Purdue Peg Board, or general intelligence (45) (also Siever, unpublished data).

Thus, schizotypal individuals manifest deficits in executive function, working memory, verbal learning/episodic memory, and attention but not generalized intellectual, perceptual, and motor deficits. These impairments may point to the involvement of specific brain systems. For example, prefrontal cortex, particularly dorsolateral prefrontal cortex, has been implicated in both animal and human studies of executive function such as WCST and visuospatial delayed response or “working memory” (50, 54), while temporal cortical regions have been implicated in verbal learning. Frontostriatal circuits play a central role in modulating sustained attention. These studies also suggest that circuitry involving critical cortical areas such as frontal and temporal cortex may be compromised in SPD subjects.

Structural Imaging

Temporal cortex, frontal cortex, striatum, and thalamus, have been particularly implicated as regions of interest in the schizophrenic disorders (see Table 3). CSF volumes are generally increased and cortical volumes reduced in SPD (55, 56). Volume reductions in temporal cortex, particularly superior temporal gyrus, have been among the most consistent structural alterations reported in chronic schizophrenia (57-62). Reduced size of temporal cortex has also now been reported in schizotypal personality disorder, both in superior

temporal gyrus (63) and Heschl's gyrus (64) as well as in inferior and medial temporal gyri (62, 63), and these reductions have been associated with schizophrenia-related psychopathology (62). Studies of relatives of schizophrenic patients also suggest reductions in medial temporal regions including the amygdala/hippocampal complex (63, 65). These findings are thus consistent with a model of common temporal abnormalities across the schizophrenia spectrum. Frontal cortical volume, on the other hand, appears to be relatively preserved in initial studies of schizotypal personality disorder (66), while reductions in frontal volume have been found in many but not all studies of schizophrenic patients. However, relative reductions in frontal volume are correlated with the deficit-like symptoms of schizotypal personality disorder in healthy volunteers implying patients with lower frontal volume will be more likely to display traits such as asociality (67, 68). While a number of factors extrinsic to the illness itself including sustained neuroleptic treatment, alcohol abuse (rare in SPD), or chronic psychosis might contribute to the differences between SPD/normal and schizophrenia/normal comparisons of frontal cortical volumes, these factors could not easily explain the fact that temporal regions are comparably reduced in both schizophrenia and SPD. The finding of normal frontal volume, however, in SPD requires replication.

The thalamus is a critical nodal link that integrates diverse circuits in the brain including incoming sensory information with higher cortical regions involved in planning response strategies. The thalamus as part of circuitry including cortex and cerebellum has been hypothesized to play a central role in the pathophysiology of schizophrenia and this hypothesis is supported by post-mortem (69-71) and imaging studies (60, 72, 73). The thalamus encompasses a number of distinct nuclei which have partially different patterns of connectivity to other brain regions. For example, the pulvinar, which has close connections with temporal lobe structures, is reduced in SPD subjects as it is in schizophrenic patients compared to normal controls, while the volume of the medial dorsal nuclei, associated with prefrontal cortex, is not reduced in schizotypal patients compared to normal controls in contrast to the reductions observed in schizophrenic patients (72). Thus, reductions in the subcortical nuclei relaying from thalamus to cortex seem to parallel reductions in associated cortical regions in SPD, i.e., temporal, but not frontal volume reductions.

The striatum and its connections to cortex have also been implicated in schizophrenia, in part, because dopamine is a key neurotransmitter in these regions and striatal structures are a major target of the neuroleptic medication's D₂ antagonism. Compensatory increases in dopaminergic dendritic structures following long-term neuroleptic administration are believed to account largely for

striatal volume increases that have been rather consistently reported in schizophrenic patients (60, 74-76). These considerations suggest that under circumstances of altered dopaminergic activity, changes in striatal volume may partially reflect dopaminergic activity. In never medicated schizophrenic patients, striatal volumes may be normal or even slightly reduced. Striatal volumes have been found to be reduced in schizotypal patients compared to normal controls and schizophrenic patients. While these differences could in principal be due to differences in degree of past neuroleptic use, even never-medicated schizotypal patients have demonstrated significantly reduced striatal volume compared to both never-medicated schizophrenic patients and normal controls (76, 77) (see Table 3). In another study, reduced caudate volume was found in SPD subjects compared to controls (77). While these studies can not directly address dopaminergic function, neuroleptic induced striatal volume increases appear likely to be due to proliferation of dopaminergic dendrites or mitochondria (74). Thus, the reduced striatal volume in schizotypal patients might be compatible with reduced dopaminergic activity in schizotypal compared to schizophrenic individuals.

Table 4: Functional Imaging

	Chronic Schizophrenia		Schizotypal Personality Disorder	
	Character of Abnormality	Effect Size	Character of Abnormality	Effect Size*
Frontal Lobe Activation	Metabolic rate reduced in most, increased in some	Variable, small-medium(79,125,126)	Increased activation in middle frontal gyrus	Medium(78,79)
Temporal Lobe Activation	Metabolic rate increased in majority of studies, but decreased in others	Variable, medium (right)- large (left)(79,125,127)	Reduced compared to controls, but not to as great a degree as schizophrenic patients	Small(78,79)
Striatal Activation	Metabolic rate reduced in ventral putamen	No significant difference from controls(76)	Metabolic rate significantly elevated in ventral putamen	Small, medium between SPD patients and schizophrenic patients, unmedicated and total(76)

* SPD effect sizes based upon a small number of studies (generally 1-3), so confidence interval is limited

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Variable: inconsistent results across studies

Functional Imaging

Numerous imaging studies in schizophrenia suggest reduced and/or anomalous activation of cortex, primarily frontal cortex. In a SPECT study measuring blood flow conducted in our laboratory, schizotypal patients performing the WCST showed lower activation in left middle frontal gyrus but greater activation in other regions of the brain, particularly in right prefrontal cortex, than control subjects. These results suggested that patients with SPD were less effective in activating prefrontal regions that normals activate to efficiently accomplish the task. However, the schizotypal subjects did activate other prefrontal brain regions, such as right prefrontal cortex, not activated in healthy volunteers, possibly as a compensatory mechanism to offset the reduced efficiency in left prefrontal cortex (78, 79).

In a FDG PET paradigm measuring brain glucose metabolism, schizotypal patients demonstrated a pattern of altered temporal lobe utilization in laterality similar in character but not as severe as that observed in schizophrenic patients (78, 79). New BOLD fMRI data from our laboratory (80) also suggests that SPD patients do not activate dorsolateral prefrontal cortex to the degree normal control subjects do, while they do activate Brodmann area 10 to a greater degree than controls. These results suggest compensatory activation of prefrontal regions other than those employed by normal controls in the schizotypal patients. They are consistent with the possibility that SPD patients are better able than schizophrenic patients to use frontal reserves to compensate for inefficiency of task performance.

The FDG PET study performed in our center also focused on striatal structures. Significantly increased metabolic activity was found in ventral putamen, an area rich in D₂ receptors, in SPD subjects compared to schizophrenic patients and normal controls (76). As these D₂ receptors mediate dopaminergic inhibition of putamen activity, these results raised the possibility of reduced dopaminergic modulation of the putamen. This increased activation was also seen in never-medicated schizotypal patients compared to never-medicated schizophrenic patients, suggesting that the difference between SPD and

schizophrenic subjects was not an artifact of different medication histories. Greater activation was associated with less psychotic-like SPD symptoms, while reduced activation (possibly reflecting greater dopaminergic inhibition) was associated with greater psychotic-like symptoms (76).

In summary, functional imaging studies suggest activation patterns in cortex in SPD subjects display similar anomalies to those observed in schizophrenic patients but to a lesser degree (Table 4). Furthermore, the presence of compensatory activity in frontal lobe may diminish the functional impact of reduced activation in temporal or other cortical regions. Metabolic activity appears increased in ventral striatum possibly associated with reduced dopamine inhibition.

Neurochemistry

Due to the profound influence of the dopamine hypothesis of schizophrenia, based largely on the efficacy of neuroleptic medication, neurochemical studies of schizotypal individuals initially focused on dopamine and its metabolites in cerebrospinal fluid (CSF) and plasma. Decreased dopamine metabolites have been reported in schizophrenic patients with poor prognosis and moderately severe social impairment and increased dopamine metabolites with greater psychotic symptoms (81). In the first report from our laboratory, CSF homovanillic acid (HVA) was found to be increased in schizotypal patients compared to normal controls.

Table 5: Neurochemistry/Neurochemical Imaging of Dopamine System

	Chronic Schizophrenia		Schizotypal Personality Disorder	
	Character of Abnormality	Effect Size	Character of Abnormality	Effect Size *
DOPAMINE Metabolites CSF	Normal to low, negatively correlated with cortical atrophy	Variable; N/A for most studies, medium in one study showing decreased CSF HVA in schizophrenic patients(81,122)	Increased in one study compared to patients with other personality disorders, as well as historical controls and attributable to psychotic-like symptoms	Variable: Large in one study of SPD patients with psychotic-like symptoms(82)
Plasma	Decreased in poor prognosis, negatively correlated with deficit symptoms, positively correlated with total symptoms	Variable, $r = .66 \pm .10$, $p < .002$ No effect size applicable, correlational relationship only(81,84,85)	Increased compared to normal controls and patients with other personality disorders and attributable to psychotic-like symptoms, in clinical patients, reduced in SPD relatives of schizophrenic patients with deficit-like symptoms	Variable: Large for SPD patients with psychotic-like symptoms(83)
Response to Amphetamine Clinical	Variable, including both worsening of psychosis, and improvement of deficit symptoms	+ 25% +/- 35% change in positive symptoms, - 10% +/- 20% change in negative symptoms(123)	Lessening of both positive and negative symptoms	-7 +/- 23% change in positive symptoms, -25 +/- 20% in negative symptoms(123)
D₂ Displacement	Increased	Large(87)	Increased (compared to normal controls) Decreased (compared to schizophrenic patients)	Large for both comparisons(123)
Response to Deoxyglucose (2DG)	Plasma HVA increased ACTH increased Cortisol normal	Plasma HVA effect size is large, ACTH effect size is large(90,91)	Plasma HVA normal ACTH normal Cortisol significantly lower than in normal controls	Cortisol effect size is large(124)

* SPD effect sizes based upon a small number of studies (generally 1-3), so confidence interval is limited

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However, this increase was entirely accounted for by the psychotic-like symptoms of the disorder and covarying for these symptoms abolish the difference. Furthermore significant correlations were found between CSF HVA activity and these psychotic-like symptoms of schizotypal personality disorder (82).

Similar results were obtained in studies in our center utilizing plasma HVA as an index of dopaminergic activity. Plasma HVA concentrations were increased in schizotypal patients compared to normal controls or patients with other personality disorders and these increases were correlated with the number of psychotic-like symptoms but not other deficit-related schizotypal symptoms. Covarying for these symptoms similarly nullified the differences between groups (83).

Plasma HVA concentrations were also determined in relatives of patients with schizophrenia (84, 85). These relatives either were diagnosed with schizotypal personality disorder, other non-schizophrenia related personality disorder, or had no diagnosis. The schizotypal relatives of the schizophrenic patients had reduced plasma HVA concentrations compared to those relatives with other personality disorder diagnoses or no diagnosis. In this case, the deficit-like symptoms, which are more prominent in relatives of schizophrenic patients than the psychotic-like symptoms (5), accounted for the findings of reduced HVA concentrations. Covarying for negative deficit-like symptoms rendered any differences insignificant and significant correlations were found between the extent of deficit-like symptoms and reduced HVA concentrations. After residualizing the variance of negative or deficit-like symptoms, the positive correlation between HVA concentrations and psychotic-like symptoms emerged just as in the clinical patients. While plasma concentrations derive from both peripheral and central sources, under usual conditions the peripheral component is correlated with the central component (86) suggesting that these differences in

correlations may reflect in part central differences. Furthermore, in this personality disorder cohort, CSF and plasma HVA were highly positively correlated (67) (Table 5).

The convergence of the CSF and plasma HVA studies suggest that higher dopaminergic activity may be associated with greater psychotic-like symptoms and reduced dopaminergic activity may be associated with greater deficit-like symptoms in SPD patients. Group differences may emerge when one or the other symptom domains predominates, but the correlations between symptom clusters and HVA concentrations are the most consistent finding in these studies of HVA. Indeed, these results are consistent with studies of schizophrenic patients suggesting that reductions of dopaminergic activity in prefrontal cortex are associated with the deficit symptoms and cognitive impairment of schizophrenia and increased activity in subcortex is associated with the psychotic symptoms of schizophrenia (81). Studies of SPD may permit a clearer dissociation of these two relationship roles in SPD than is easily possible in chronic schizophrenia, where deficit and psychotic symptoms may be more highly correlated as a function of severity of illness.

Neurochemical Imaging

More direct assessment of neurotransmitter functions, such as dopamine, in specific brain regions, is possible with neurochemical imaging paradigms utilizing SPECT or PET. For example, dopamine release from striatum can be evaluated following the administration of a single dose of amphetamine and measuring displacement of radiolabeled [^{123}I] IBZM, which labels D_2 receptors in striatum. The degree of IBZM displacement or percent reduction in binding can then be used as a measure of dopamine release stimulated by amphetamine. A similar paradigm using the D_2 ligand raclopride's displacement by dopamine release in PET scans has also been applied to schizophrenic patients (87). Amphetamine induces greater dopamine release in schizophrenic patients than in normal comparison subjects in several independent studies using either a SPECT-IBZM protocol (88) or PET-raclopride protocol (87). The degree of dopamine release following amphetamine is associated with worsening of psychotic symptoms in response to the amphetamine in these studies. These results suggest that in acute schizophrenic patients, stimulated dopamine release is greater than in normal controls and this may be associated with their acute psychosis. More recent results measuring basal dopaminergic activity using alpha-methylparatyrosine (AMPT) to deplete available dopamine and measuring increases in raclopride following AMPT suggest that basal dopaminergic activity is similarly increased in schizophrenic patients and is indeed correlated with the extent of amphetamine-stimulated release.

In contrast, in a study of schizotypal personality disorder patients using the IBZM SPECT paradigm, IBZM displacement following amphetamine in SPD was significantly less than that observed in schizophrenic patients, although modestly but significantly increased above that of normal control subjects (89). No worsening of psychotic-like symptoms was seen in any of the schizotypal patients studied following the amphetamine administration and improvement in negative symptoms was observed in the total cohort and even in positive symptoms in some patients (Table 5). While the plasma and CSF measures of dopamine metabolism were assessed in populations of SPD patients with more prominent psychotic-like symptoms and were correlated with psychotic-like symptoms, the patients in this study had a range of symptoms but deficit symptoms were more prominent. These studies cumulatively suggest that there may be variable dopaminergic activity in SPD that may be directly associated with extent of psychotic-like symptoms and inversely with deficit-like symptoms.

Response to stressors such as the administration of 2-deoxyglucose (2-DG), a glycolytic stressor, results in increases in dopamine release in subcortex reflected in increases in plasma HVA and as well as increases in ACTH and cortisol. Schizophrenic patients show increased plasma HVA and ACTH responses to 2-DG compared to normal controls (90, 91). In contrast, patients with SPD show plasma HVA concentrations in response to 2-DG comparable to that of normal controls in a similar 2-DG protocol as that utilized in the study of schizophrenic patients (92). These results suggest that while schizophrenic patients may have a greater susceptibility to subcortical dopaminergic release under stress, schizotypal individuals do not show this increased response suggesting better “buffering” of the subcortical dopamine system in this disorder. Thus, dopaminergic indices do not appear to be consistently increased in prototypic SPD patients who have not exhibited frank psychotic symptomatology in contrast to schizophrenic patients, in which direct measures of release correlate with psychotic exacerbation.

A Pathophysiologic Model of the Spectrum Disorders

The results of the various studies reviewed above, coming from diverse investigative perspectives, suggest not only that there may be partially distinct susceptibilities to the schizophrenia spectrum and psychosis but also hint at the beginnings of an understanding of the underlying pathophysiologic processes underlying each. We thus propose a model based on these data that can generate testable hypotheses for future research. In this model, schizotypal and schizophrenic individuals are hypothesized to share a common genetic anomaly

that render temporal cortex particularly vulnerable to environmental insults such as hypoxia. However, genetic factors independent of the vulnerability to the schizophrenia spectrum *per se* and/or more favorable environmental influences would leave the schizotypal individual better buffered with regard to frontal volume and function as well as stabilization of subcortical dopaminergic activity. Thus, genetic and environmental factors that determine phenotypes which are partially distinct from those factors directly associated with the susceptibility to schizophrenia, e.g. frontal reserve capacity or at a cognitive level, general intelligence, serve as mitigating factors in SPD, diminishing the impact of the genetic susceptibility genes to schizophrenia. These modifying factors may play an important role in determining whether a susceptible individual develops chronic schizophrenia or a milder spectrum condition, with potentially important implications for early intervention and treatment.

This model of the pathophysiology of the schizophrenia spectrum disorders posits that the social deficits and cognitive impairment characteristic of the entire spectrum of schizophrenia related disorders is the result of an underlying genetic diathesis that in conjunction with modifying environmental factors adversely affects cortical structures such as temporal and prefrontal cortex. These structures may be particularly sensitive to developmental aberrations such as altered migration of neurons, aberrant dendritic growth patterns, or alterations in the compaction and maintenance of the myelin sheaths of axons with subsequent disconnection between critical brain regions. Temporal and related lateral cortical regions represent logical sites that may be impaired across the schizophrenia spectrum disorders for the reasons elucidated below.

As cited in the above overview, temporal volume reductions and functional abnormalities are among the most consistently observed findings in schizophrenia (58, 59). These abnormalities are hypothesized to constitute a primary “spectrum” abnormality, (i.e., present across the entire spectrum of schizophrenia-related disorders), and are associated with the core symptomatology and cognitive impairment of the schizophrenic disorders. This pathology might emerge from genetic susceptibilities interacting with adverse environmental events such as hypoxia from birth complications, which represent a risk factor for the schizophrenia-related disorders (93). An animal model of schizophrenia suggests that neonatal lesions in ventral hippocampus, which represents a medial temporal structure, can cause a number of abnormalities in the adult rat that resemble the clinical signs and symptoms of schizophrenia (94). Animals with these lesions demonstrate locomotor hyperactivity after pharmacologic stimulation with agents such as amphetamine or NMDA antagonists and after stress paradigms associated with altered subcortical

dopaminergic responsiveness as well as social deficits. These effects appear to be mediated by prefrontal cortical neurons and the vulnerability to these behavioral consequences depends in part on genetic factors (95). Along these lines, in twins discordant for schizophrenia, hippocampal volume reductions are significantly correlated with cognitive dysfunction in the Wisconsin Card Sort Test (WCST) mediated substantially by frontal lobe (96). This model would therefore predict that temporal lobe and hippocampus would be among the most consistent regions displaying reduced volume across the schizophrenia spectrum disorders including SPD with consequences for frontal function. SPD patients could be protected from the downstream effects of abnormalities in these lateral structures by compensatory strengths in intrinsic frontal functional capacity and/or greater intrinsic stability of subcortical structures (Figures 1, 2).

While schizophrenic patients show volume reductions in frontal lobe in many but not all studies, SPD subjects exhibit normal to increased frontal lobe volumes in the limited data available (79). In this model, we propose that greater frontal reserves in schizotypal personality disorder compared to schizophrenia protect the schizotypal individual from the severe cognitive deterioration and social deficits associated with chronic schizophrenia. Schizotypal individuals may also be able to better use their frontal capacities, perhaps by compensating for dysfunction in regions such as dorsolateral prefrontal cortex (DLPFC), utilized by healthy volunteers to accomplish working memory and executive tasks, by activating other frontal regions not normally recruited by normal volunteers (79). Thus, schizotypal individuals would be more resistant to the downstream effects of temporal pathology. This model predicts that frontal volumes would be more preserved in schizotypal subjects than in schizophrenic subjects and that schizotypal individuals would be able to activate compensatory prefrontal regions. In contrast, normal volunteers do not need to activate these regions, whereas schizophrenic patients, unlike schizotypal individuals, are unable to substantially compensate for DLPFC dysfunction by activating supplemental brain areas in order to compensate for dorsolateral prefrontal cortical dysfunction.

The thalamus, a nodal way station linking diverse regions of the brain, has been hypothesized to play a central role in the altered circuitry in schizophrenia (97). The finding of reduced pulvinar volume in SPD, as also observed in schizophrenic patients, and unchanged medial dorsal nucleus volume, in contrast to the reduced volume of this region in schizophrenic patients, suggests that abnormalities in these thalamic nuclei parallel those of their cortical projections and implicate the temporal cortex and pulvinar as part of circuitry that is impaired across the schizophrenia spectrum disorders while prefrontal circuitry is impaired primarily in schizophrenia.

Finally, subcortical structures which are modulated by frontal cortex may be better protected from the impact of relative dysfunction of frontal cortex and functional deafferentation of subcortical structures in schizotypal compared to schizophrenic subjects, both because frontal function is better preserved and/or because intrinsic dopamine activity in striatum may be more effectively regulated. Lesions of prefrontal cortical dopamine systems or disconnection of frontal cortex and striatum result in upregulation of subcortical dopaminergic activity with increases in presynaptic dopamine release and dopamine receptor sensitivity (98, 99) providing a possible animal analogue of frontal cortical hypodopaminergia leading to subcortical dopaminergic overactivation in schizophrenia (Figure 1). Different rodent strains vary in the degree of upregulation observed in response to these kinds of perturbations (99). Comparable individual differences between people might also modulate the degree to which striatal dopaminergic upregulation occurs in the face of frontal dysfunction, for example, as may be induced by stress paradigms (90) or secondary to functional reductions in frontal dopaminergic activity. Schizotypal individuals may be constrained in their capacity for upregulation of subcortical dopaminergic activity (1), secondary to differences in intrinsic subcortical dopaminergic activity, receptor regulation, or other key modulator systems such as the glutamate system. Thus, they may be less likely to upregulate subcortical dopaminergic systems than schizophrenic patients in response to frontal hypodopaminergia protecting them from the emergence of overt psychosis (Figure 2).

This hypothesis is consistent with findings of reduced release of dopamine in subjects with SPD compared to schizophrenic patients following pharmacologic releasing agents such as amphetamine (88, 89) or stressors that perturb dopaminergic activity (92). Furthermore, it would suggest that psychotic-like symptoms would not worsen in SPD patients following amphetamine administration and might even be accompanied by improvement of deficit symptoms in subjects with SPD, as has been observed in studies of SPD without comorbid BPD using oral amphetamine (100, 101).

This model also allows an evaluation of intermediate phenotypes or endophenotypes that may more likely have underlying genetic foundations and to be associated with specific brain dysfunction in schizophrenia (21, 47). If intermediate phenotypes could be identified at a neurobiologic level as, for example, a specific psychophysiological, biochemical, or cognitive abnormality, we may be more successful in identifying the underlying genes for the schizophrenic syndrome. Phenotypes characterized by asociality, cognitive disorganization, and restricted affectivity, traits that are common to the entire spectrum of

schizophrenic disorders, might reflect a genetic impairment, particularly prominent in temporal or hippocampal regions, that is common to the entire schizophrenia spectrum.

One promising example of an endophenotype that is intermediate between the genotype and clinical phenotype is the P50 suppression abnormality, which is associated with the alpha-7 nicotinic receptor gene in relatives of schizophrenic patients and reflects an abnormality in sensory gating or filtering function of the hippocampus, where these receptors are localized (19). Another intermediate phenotype may be more characterized by severe executive dysfunction and failure of planning and abstraction related to aberrant frontal activity and observed in more chronic, but not necessarily acute forms, of schizophrenia or to the same degree in schizotypal individuals. For example, a common allele (the Val allele) of a functional polymorphism (Val(108/158)Met) for catecholamine-O-methyltransferase (COMT), the major enzyme for extraneuronal metabolism of dopamine, is associated with increased activity of COMT compared to the lower activity form of COMT coded by the Met allele, thus resulting in relatively reduced availability of dopamine in prefrontal cortex. The Val allele is associated with greater perseverative errors on the WCST and poorer performance on the N-back CPT reflecting deficits in executive function and working memory and thus working memory impairment may serve as an endophenotype for a gene that appears to account for a modest but significant proportion of the variance for the susceptibility to schizophrenia (54) and may be associated with schizotypal personality disorder in preliminary studies (102). Finally a third intermediate phenotype may be characterized by psychosis without necessarily outstanding prefrontal cognitive impairment or deficit symptoms, related to underlying increased subcortical dopaminergic activity. Candidate genes related to dopamine activity such as the genes for dopamine beta-hydroxylase (103, 104), a key biosynthetic enzyme for dopamine, or the dopamine D4 receptor (DRD4) (105, 106), have been associated in these studies with psychosis per se rather than specifically schizophrenia. While these examples are certainly not definitive, they illustrate the power of a multifactorial or multidimensional perspective applied to candidate genes and intermediate phenotypes in schizophrenia.

These phenotypic dimensions may be interactive so that, for example, the predispositions to neurodevelopmental aberration in hippocampus or temporal cortex, frontal dysfunction, and psychosis may interact synergistically to increase the probability of developing schizophrenia while hippocampal impairment might lead to P50 abnormalities and perhaps spectrum pathology but not necessarily schizophrenia. Vulnerability and protective factors within a single domain, e.g. hippocampal function, may also be interactive so that, for example, relatives of

schizophrenic probands with P50 abnormalities have been found to have larger hippocampi than those without the P50 abnormality consistent with the hypothesis that larger hippocampi reflecting increased processing capacity may partially compensate for the sensory gating deficit in these relatives protecting them from schizophrenia (107). Available data testing multiple endophenotypes in the same subjects with spectrum pathology suggest that endophenotypes such as P50 and pre-pulse inhibition are distinct in that they do characterize different subpopulations (108). A better understanding of these partially distinct pathophysiologic processes as they manifest themselves across the schizophrenia spectrum may help point to new promising endophenotypes and candidate genes, and help clarify how they interact.

Future Directions

The study of schizotypal personality disorder has begun to provide new opportunities to disentangle the genetics and pathophysiology of schizophrenia. By contrasting and comparing schizotypal, schizophrenic, and healthy volunteer subjects, commonalities and distinctions between schizotypal personality disorder and schizophrenia are being mapped using neurochemical, imaging, and pharmacologic tools. As arrays of candidate genes begin to be identified in relation to schizophrenic disorders, those genes that are associated with both schizotypal and schizophrenic disorders and those that are unique to schizophrenia and psychosis could be identified. Clusters of schizotypal traits and/or cognitive dysfunctions may be used to provide intermediate phenotypes to more finely hone our understanding of the character of genetic/phenomenologic relationships in the spectrum. Furthermore, schizotypal personality disordered individuals also afford a unique opportunity to pilot pharmacologic interventions that might serve to enhance cognitive function or improve negative symptoms, because these individuals have more reversible cognitive and social deficits than chronic schizophrenic patients and are less vulnerable to potential worsening of psychosis.

Table references:

Psychophysiology:

1. SPEM (28, 29, 31)
2. Antisaccade (29)
3. Backward Masking (109)
4. P50 (19, 20)
5. P300 (26, 27)
6. N400 (24, 25)
7. Prepulse Inhibition (22, 23)
8. Latent Inhibition (37-39)
9. Negative Priming (40-42)
10. all of the above for the most part: (47)

Cognitive:

1. Working memory visuospatial (34), (44, 50)
2. Working memory auditory (34, 44, 48)
3. Episodic memory (34), (44)
4. Verbal Learning (34), (44), (51)
5. CPT (33), (35), (34)
6. WCST (45), (110),(47), (34)
7. Trail B (34), (44), (45, 111)
8. WAIS Vocab (112), (45), (51), (44)
9. WAIS Block (34), (44), (45), (51)

Structural Imaging:

1. Whole Brain (75)
2. Frontal (113), (60), (61)
3. Temporal (58), (60), (61), (62)
4. STG (59, 63), (62), (60), (61)
5. Medial (61), (63)
6. PT (114)
7. HG (64), (114)
8. ACG (115), (116)
9. Parietal (117), (58), (118)
10. Occipital (60), (117), (58)
11. Putamen (76), (60)
12. Caudate Nucleus (75),(77)
13. Thalamus (72), (73), (60)
14. MDN and Pulvinar same as above
15. Cerebellum (75)

16. CC (119)
17. CSP (58), (120), (121)
18. CSF (55), (117)
19. LTH (60)
20. LV (75), (60)
21. TV (75), (60)
22. FV (58), (60)

Neurochemical Imaging

1. CSF (81) (82, 122)
2. Plasma (81), (83), (85), (84)
3. Clinical response (123)
4. D2: (87, 123)
5. 2DG (124), (90), (91)

Functional Imaging

1. Frontal Lobe (125), (78), (126) (79)
2. Temporal Lobe (125), (78), (127) (79)
3. Striatal Activation (76)

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