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Schizotypal Personality Disorder: A Current Review

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Abstract

The study of schizotypal personality disorder (SPD) is important clinically, as it is understudied, challenging to treat, often under-recognized or misdiagnosed, and associated with significant functional impairment. SPD also represents an intermediate schizophrenia-spectrum phenotype, and therefore, can provide a better understanding of the genetics, pathogenesis, and treatment of related psychotic illnesses. In this review we discuss recent findings of SPD related to epidemiology and functional impairment; heritability and genetics; working memory and cognitive impairments; social-affective disturbances; and neurobiology. Additionally, we examine the challenges associated with treating patients with SPD, as well as clinical recommendations. Finally, we address future directions and areas in need of further exploration.

Keywords

Schizotypal; schizophrenia; personality disorder; frontal lobe; temporal lobe; dopamine; working memory; cognition; social cognition; affect processing; magical thinking; perceptual aberration; suspiciousness; paranoia; social anhedonia

Introduction

Introduced in DSM-III, the diagnostic construct of schizotypal personality disorder was derived from two converging lines of investigation: 1) borderline personality conditions, which represented a clinically identified and heterogeneous population of functionally impaired patients that manifested a variety of pervasive disturbances of interpersonal function, cognition, affect, and behavioral control, many of whom exhibited attenuated

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schizophrenia-spectrum traits; and, 2) studies of non-psychotic family members of patients with schizophrenia who exhibited chronic peculiarities of thought and communication, as well as impoverished social function. Accordingly, early studies of the SPD construct were either related to: 1) confirmation of its utility in identifying non-clinical individuals carrying a genetic vulnerability to schizophrenia; or, 2) clarification of its clinical validity, particularly in comparison with the borderline personality disorder (BPD) construct. Therefore, the significance of defining the diagnosis of SPD was two-fold: It was an important step in the refinement of present-day severe personality disorder syndromes; and, it has yielded an operational definition of an intermediate schizophrenia-spectrum phenotype that can be used to investigate the pathogenesis, genetics, and development of therapeutics of major psychotic disorders. Studies of SPD have increasingly focused on schizophrenia-spectrum issues, and there has been relatively less emphasis on SPD as a clinical syndrome, in and of itself. In this review we will discuss recent findings in SPD and schizotypy related to epidemiology and functional impairment, pathogenesis, cognitive impairment, and neurobiological findings. Additionally, clinical topics will be addressed regarding the phenomenology, differential diagnosis, multidimensionality, and treatment considerations.

Diagnostic Criteria, Psychometric Structure, and Multidimensionality

The SPD diagnostic criteria for DSM-5 are essentially unchanged from DSM-IV-TR, and consist of: ideas of reference; odd beliefs or magical thinking; unusual perceptual experiences and bodily illusions; odd thinking and speech; suspiciousness or paranoid ideation; inappropriate or constricted affect; behavior or appearance that is odd, eccentric, or peculiar; lack of close friends or confidants, other than first-degree relatives; excessive social anxiety that doesn't diminish with familiarity and tends to be associated with paranoid fears. Five of nine criteria are required for a diagnosis of SPD.

SPD (as well as schizotypy in non-clinical populations) has consistently been shown to be a multi-dimensional construct. Although not all studies are in agreement, analyses of SPD have most consistently revealed a 3 factor solution: *Cognitive-Perceptual* (‘odd beliefs,’ ‘perceptual disturbances,’ ‘ideas of reference,’ and ‘paranoia/suspiciousness’), *Interpersonal* (‘no close friends,’ ‘social anxiety,’ +/-‘restricted affect’), and *Disorganized/Oddness* (‘odd speech/thought,’ ‘odd behavior,’ -/+ ‘restricted affect’). Assignment of ‘restricted/ inappropriate affect’ to either the *Interpersonal* or *Oddness* factor appears to depend on whether assessment was performed by 1) self-report in non-clinical populations, as opposed to 2) semi-structured interview of SPD or personality disordered patients, respectively[1]. Therefore, as our focus is on clinical populations, and given the greater validity of personality assessment from semi-structured interview compared to self-report, we favor the inclusion of ‘restricted affect’ in the *Oddness* domain. More recently, four dimensional factors were resolved among non-psychotic family members of schizophrenia probands, consisting of: *Negative Schizotypy*, *Positive Schizotypy*, *Interpersonal Sensitivity*, and *Social Isolation/Introversion* [2]. This four factor solution is similar to one described using a self-report measure of schizotypy among non-clinical participants [3].

Recent findings however have indicated that despite the validity of such a 3-factor solution among the 9 diagnostic criteria of SPD criteria, only the *Cognitive-Perceptual* and *Oddness*

factors persisted when examining the factor among *all* DSM-IV personality disorder criteria. Moreover, when all DSM-IV personality disorder criteria were examined, 'paranoia/ suspiciousness' was associated with a factor that essentially consisted of Paranoid Personality Disorder (PPD) criteria; 'no close friends' was associated with the same criteria from Schizoid Personality Disorder (SCPD); and, 'social anxiety' was not related to any clinically coherent factor. Moreover, the social anxiety and no close friends criteria of SPD were significantly correlated with a number of personality disorder diagnoses. Thus, the *Interpersonal* domain (a well as 'paranoia/suspiciousness') did not appear to be useful in discriminating SPD from other personality disorders. Cognitive-Perceptual criteria (namely, ideas of reference, odd beliefs, and perceptual disturbances) have been shown to exhibit high sensitivity and moderate positive predictive value (PPV) in terms of diagnosis of SPD; Oddness criteria (odd behavior, odd speech/thought process, and restricted affect) exhibited the highest PPV for the SPD diagnosis.

Epidemiology and Functional Impairment

The lifetime prevalence of SPD in the United States (US) has recently been estimated to be just under 4%, with slightly higher rates among men (4.2%) than women (3.7%). Likelihood of SPD was greater among black woman, those with a low income, and people who were separated, divorced, or widowed; and, odds of SPD were lower in Asian men. After adjusting for sociodemographic parameters and comorbidities, SPD remained significantly associated with bipolar I and II disorders, PTSD, BPD, and narcissistic personality disorder (NPD). Additionally, even after adjusting for sociodemographic parameters and Axis I and II comorbidities, patients with SPD had significantly greater disability than those without SPD [4].

Among a large, Norwegian cohort of treatment-seeking personality disordered patients, 1.37% of patients met criteria for SPD, and 21% reported at least 2 SPD symptoms. One-third of SPD patients were not comorbid with any other personality disorder, one-third had only one additional comorbid personality disorder, and one-third of SPD patients were diagnosed with two or more additional personality disorders. In addition to PPD, antisocial personality disorder (ASPD) also occurred with greater frequency among patients with SPD compared to the total sample of personality disordered patients. Although Cognitive-Perceptual criteria of SPD were strongly associated with a diagnosis of BPD, BPD occurred with no greater frequency among patients with SPD than the total sample of personality disordered patients. SPD exhibited a stronger association with obsessive-compulsive disorder (OCD) than other personality disorders [1].

While it is clear that SPD is a clinically and functionally disabling condition, the basis of functional impairment and its relation to other phenomenologically similar personality disorders has not been fully elucidated. In terms of 'real world' functioning, patients with SPD have been shown to be less likely to live independently or have obtained a Bachelor's degree than patients with avoidant personality disorder (AvPD) and healthy control participants. Both patients with SPD and AvPD earned a lower hourly wage compared to healthy control participants, however. Using an interview-based assessment of functional capacity (UCSD Performance-Based Skills Assessment or UPSA), SPD patients

demonstrated lower functional capacity than patients with AvPD and healthy control participants. Similar to the role of cognitive dysfunction (working memory, processing speed, executive function) as a major determinant of functional outcomes in schizophrenia, functional capacity in patients with SPD was shown to be significantly correlated to a composite measure of cognitive function. Similar to previous reports, cognitive function among SPD patients was shown to be poorer than among healthy control participants and patients with AvPD [5].

Similar results have been found when examining patients with SPD, PPD, SPD and PPD (SPD/PPD), compared to participants without either of these diagnoses. A diagnosis of SPD or PPD was associated with cognitive impairment, and comorbidity of SPD and PPD was not associated with worse cognitive performance over and above either disorder, alone. While a diagnosis of either SPD or PPD was associated with less likelihood of employment than patients without either of these diagnoses, these differences were found to be primarily determined by cognitive impairment. Even after adjusting for cognitive function, however, a diagnosis of SPD was associated with employment at jobs involving less social contact; and a diagnosis of PPD was associated with lower likelihood of having a history of competitive work for more than a year [6].

Pathogenesis of SPD

Heritability of SPD

Early studies revealed that SPD was more common among the relatives of schizotypal probands, compared to those of families with non-Cluster A personality disorders [7]. Twin studies have provided evidence that SPD is determined by both familial-genetic and unique environmental factors [8;9]. It has also been observed that SPD can manifest in 3 different phenotypic classes, which are associated with differing etio-pathogenic paths [10]. A prominent genetic contribution was associated with a phenotypic class of SPD that exhibited exceptionally high levels of odd appearance/behavior, restricted affect/aloofness, as well as lack of close friends. A second SPD class, marked by high levels of magical ideation and perceptual disturbances, was also determined by familial-genetic and unique environmental influences. A third SPD class, however, consisting of moderately high levels of ideas of reference, social anxiety, and suspiciousness, but low levels of odd behavior, odd speech, and constricted affect, did not exhibit heritability, but rather, appeared to be determined entirely by unique environmental influences. In addition to the categorical diagnosis of SPD, the heritability of psychometric schizotypy and associated dimensions has been examined in non-clinical populations. These reports have demonstrated that there are both liability factors that are common and specific to the various schizotypy measures/dimensions, that are determined by genetic and unique environmental influences.

Environmental Factors

Unique environmental factors (i.e., those not shared among all siblings) are strongly suggested to be involved in the development of SPD, schizotypy, and specific schizotypal dimensions. Similar to findings in schizophrenia, prenatal insults, such as influenza exposure during the 6th month of gestation (specifically, week 23) have been associated

with higher scores of schizotypal traits in an adult male population [11]. A number of forms of psychological trauma [12;13] and chronic stress [14] have been associated with SPD. The effect of trauma on the development of schizotypal symptoms, however, appears to be dependent on genetic background. For example, self-reported trauma was associated with schizotypal symptoms in first-degree relatives of schizophrenic, but not bipolar, patients [15]. Further, this effect was specific for positive schizotypal symptoms [15], consistent with the presence of specific liability factors for particular schizotypy dimensions. Interestingly, among family members of patients with bipolar disorder, self-reported trauma was associated with increased schizotypal symptoms, but only in those carrying a variant of the catechol-O-methyl transferease (COMT) associated with greater dopamine degradation [16].

Molecular Genetics

The COMT Val158Met polymorphism is one of the best studied candidate schizotypy genes. The Val allele, which is associated with greater enzymatic activity than the Met allele, has been shown to be correlated with greater levels of self-reported schizotypy [17]. There is variability as to whether susceptibility to the pro-schizotypy effects of the Val COMT occurs in non-clinical participants [17], only among schizophrenia proband family members [18], or among bipolar proband family members with high levels of psychological trauma. Moreover, while it appears the Val allele is associated with specific schizotypal dimensions, findings are mixed, as there is evidence for the Interpersonal/Negative symptoms [19;20], Cognitive-Perceptual/positive symptoms [19] Social and Physical Anhedonia [18]. Effects of the Val158Met COMT polymorphism on Disorganization symptoms have been particularly mixed, with certain studies showing a positive relationship with the Val allele [20], and others with the Met allele [21]. Lastly, multiple studies have also implicated the Val158Met COMT polymorphism in cognitive functions that have are impaired in SPD and the schizophrenia spectrum [21-23].

A number of genes, originally identified due to an association with schizophrenia, have been shown to be related to specific schizotypy dimensions and endophenotypes. Variants of the CACNA1C gene, which encodes for a protein involved in the function of L-voltage gated calcium channels, have been associated with schizophrenia and bipolar disorder. We recently performed a study determining the relationship between a CACNA1C polymorphism and schizotypal symptoms and SPD [24]. We found that the ‘A’ allele of the rs10067373 CACNA1C was associated with paranoid ideation among non-clinical, healthy participants; and was more common among patients with SPD relative to healthy control participants. Furthermore, among patients with SPD, this allele was associated with symptoms of paranoia at the level of a statistical trend [24]. In a study of a healthy, non-clinical population, common variants of the zinc-finger protein ZNF804A were associated with positive schizotypal symptoms, namely, paranoia and ideas of reference, but not negative schizotypal symptoms nor cognitive performance [25]. On the other hand, the Disrupted In Schizophrenia 1 (DISC1) gene, which is involved in neural cell development, is associated with the negative schizotypy dimension, Social Anhedonia, in healthy participants; this effect was specific, as other dimensions, such as Perceptual Aberrations and Physical Anhedonia were not involved [26]. In healthy participants, the Interpersonal

schizotypy factor has been shown to be related to variants of the p250GAP gene, which is involved in N-methyl-D-aspartate (NMDA) receptor function [27].

Neuropsychological and Cognitive Characteristics

Cognitive deficits represent one of the most functionally, clinically, and neurobiologically significant manifestations of SPD and schizotypy. Prefrontal-dependent cognitive processes -- particularly, working memory and context processing -- have received particular focus in studies of the cognitive impairments of SPD. In many ways, the intense focus on cognitive dysfunction in SPD has been largely driven by the critical role of working memory impairments on functional outcomes in schizophrenia and the lack of efficacy of standard treatments on cognitive function. Thus, characterizing working memory and other cognitive domains in SPD can allow for the assessment of novel therapeutic agents and identification of neurobiological correlates of cognitive deficits, without many of the confounds associated with such studies in schizophrenia, e.g., concurrent/past psychotropic medications, stage of illness and psychosis, chronic, severe functional impairment. However, as discussed earlier, attentional and memory difficulties are common complaints of schizotypal patients in the clinical setting, therefore, characterizing the nature of cognitive dysfunction is important for improving treatment outcomes in SPD, as well.

Studies have sought to identify relationships between schizotypal symptoms dimensions and cognitive dysfunction. We have previously demonstrated a correlation between the PASAT (Paced Auditory Serial Addition Test), an auditory, verbal working memory task that is particularly affected in SPD, and the Interpersonal symptom domain [28]. Further, it has been described that omission errors in a sustained attention span task were positively correlated with Interpersonal schizotypal traits in a non-clinical population, whereas Disorganization traits were related to false-alarm or commission errors of sustained attention [29]. However, findings have been mixed, as working memory deficits have also been shown to be related to higher levels of positive and lower levels of negative schizotypy [30].

Current pathophysiologic models of working memory impairment in SPD (and the schizophrenia-spectrum, more broadly), involve a hypodopaminergic state, particularly, in fronto-cortical regions, and subsequent understimulation of dopamine D1 receptors in the dorsolateral prefrontal cortex (DLPFC) [31]. A significant body of literature implicates the D1 receptor as a key modulator of DLPFC-dependent working memory function. Studies in neuroleptic-naïve patients with schizophrenia have described increased fronto-cortical D1 receptor availability, which is believed to reflect a compensatory, albeit insufficient, upregulation of D1 receptors owing to understimulation [32]. A relationship between greater working memory deficits and higher prefrontal D1 receptor availability in patients with schizophrenia has also been described, which has been interpreted as impaired working memory as a function of D1 receptor understimulation [33]. Unpublished studies from our group indicated that while there are no differences in fronto-cortical D1 receptor availability between patients with SPD and healthy controls, similar to what has been observed in schizophrenia, poorer working memory performance, as indexed by the PASAT, was correlated with greater prefrontal D1 receptor availability. We have previously demonstrated that the mixed D1/D2 receptor agonist, pergolide, improves working memory function in

patients with SPD [34]. Further unpublished findings from our group suggest that direct D1 receptor stimulation in SPD patients, using the high-affinity, full D1 receptor agonist, dihydrexidine, enhance working memory in patients with SPD. Although less well studied than dopaminergic mechanisms, the noradrenergic system may also be involved in the cognitive deficits of SPD. Accordingly, we have described enhancement of context processing in patients with SPD using the alpha-2a adrenergic receptor agonist, guanfacine [35].

In terms of anatomical correlates of cognitive dysfunction, we have previously described that the relationship between greater spatial working memory performance and larger ventrolateral prefrontal cortex size, observed in healthy control participants, was absent in patients with SPD [36]. The caudate or dorsal striatum, which receives input primarily from dorsolateral prefrontal regions and has been implicated in higher-order cognitive processes, appears to be involved in the cognitive abnormalities of SPD. Specifically, caudate volumes have been shown to be smaller in patients with SPD, and greater volume reduction was related to poorer cognitive performance [37]. These findings have been extended to examining more subtle changes in caudate shape abnormalities; greater aberrant morphology of the right caudate in patients with SPD was also related to cognitive impairment [38;39].

Functional imaging studies have also begun to reveal the neural substrates associated with working memory difficulties in SPD. We have previously observed attenuated working memory-associated activation of the left ventral prefrontal cortex, superior frontal gyrus, intraparietal cortex and posterior inferior gyrus in patients with SPD compared to healthy control participants [40]. In a more recent study, activation of the left posterior cingulate gyrus, and deactivation of the superior temporal gyrus, insula and middle frontal gyrus were both attenuated during a working memory task in patients with SPD compared to healthy controls [41]. Neural network synchronization, as assessed with EEG, during a visual working memory task was decreased in a non-clinical group with high- vs. low-psychometric schizotypy [42].

Social/Interpersonal and Affective Processing

A significant literature is emerging characterizing the social/interpersonal and affective dimensions of SPD and schizotypy. Pflum et al. have compared performance of two Theory of Mind (ToM) tasks in non-clinical participants selected for either high levels of positive schizotypy (Chapmans Magical Ideation and Perceptual Aberrations scales) or negative schizotypy (Chapmans Social Anhedonia scale). They found that only the positive schizotypy group exhibited ToM impairments, but specifically in a Hinting Task -- a social-*cogntive* ToM task in which participants have to infer the meaning of a fictitious character's remark [43;44]. No group differences were observed for the Reading the Mind in the Eyes Test (RMET) -- a social-*perceptive* ToM task in which participants have to infer mental states based on static visual stimuli of facial expressions that only includes peri-orbital features [43]. A measure of referential thinking, however, which is related to positive schizotypy, but not specifically Magical Ideation and Perceptual Aberrations, was associated with the RMET, such that greater levels of referential thinking were associated with poorer RMET performance [43].

Abbot et al. have performed studies similar to those described above in non-clinical participants with psychometrically determined schizotypy (using the SPQ rather than Chapman's scales) with two different tests of affect recognition [45;46]. In one study using pictures of faces with different emotions, the interpersonal factor of the SPQ (which consists of social anhedonia, constricted affect, and social anxiety) was associated with reduced accuracy of facial affect recognition; moreover, the social anxiety component of the Interpersonal factor was particularly involved in this correlation) [46]. No relationship was found, however, for the Cognitive-Perceptual SPQ factor (a measure of positive schizotypy) and facial affect recognition [46]. The same group, however, found strikingly differing results when using an affect identification task that involved more complex and dynamic stimuli, i.e., a brief audio/visual vignette of a social interaction [45]. Both total schizotypy (total SPQ score) and positive schizotypy (Cognitive-Perceptual SPQ factor) were associated with poorer recognition of positive and negative emotions [45]. However, negative schizotypy (Interpersonal SPQ factor) was only associated with impaired recognition of positive emotions [45]. The Disorganization SPQ factor was not related to emotion recognition [45].

We have recently reported a study using the Empathic Accuracy task (EA) -- a multimodal, dynamic task which assesses how well an individual's assessment of a target's affect is compared to the target's own assessment [47] -- in patients with SPD compared to healthy controls [48]. Our main finding was that the group of patients with SPD exhibited poorer performance on the EA task when assessing negative affect, compared to controls; but no group differences were observed for assessment of positive affect [48]. Moreover, the two groups did not differ on the RMET [48]. No clear association was found between severity of SPD symptoms or SPQ total or individual factor scores [48]. However, a significant effect was found, indicating greater impairment on negative valence EA performance was associated with poorer social support [48]; thus, identifying a correlate between a laboratory social cognitive test and a ‘real world’ social functional outcome.

In addition to understanding the mental states of others, studies have examined affect processing and regulation in patients with SPD, and characterized the differential contribution of the various schizotypy factors. For example, an early study by Henry et al. examined emotion regulation strategies in non-clinical participants with low and high levels of psychometric schizotypy (as assessed by the SPQ). Generally speaking, participants scoring high on the SPQ exhibited impairments in emotion amplification but not emotion suppression [49]. Moreover, it was the Negative or Interpersonal SQP factor --particularly, blunted affect -- that was associated with impaired emotion augmentation [49]. Additionally, blunted affect was shown to be associated with an increase use of emotional regulatory process, suppression [49]. Using a laboratory task assessing the effect of congruent vs. incongruent emotional primers have identifying the correct emotional valence of a target, Martin et al. demonstrated that a non-clinical group scoring high on Social Anhedonia (a Negative or Interpersonal schizotypy dimension) exhibited greater interference from incongruency of emotional valence between primer and target than did the controls or the schizotypy group scoring high on Cognitive-Perceptual traits (a Positive schizotypy dimension) [50].

Brain imaging studies have begun to shed light on the neural substrates of social/interpersonal and affective processes associated with SPD. We've recently demonstrated that patients with SPD exhibit exaggerated habituation of amygdala response to affectively valenced social visual stimuli compared to healthy control participants [51]. Premkumar et al. have characterized differences in neural activity patterns in response to social rejection in low- vs. high-schizotypy, non-clinical participants. They found that in response to social rejection activity in the dorsal anterior cingulate cortex (dACC), right superior frontal gyrus, and left ventral prefrontal cortex increased and decreased in the low- vs. high-schizotypy group, respectively [52]. Using fMRI, Soliman et al. examined the activity of striatal, cortical, and limbic regions to laboratory induced psychological stress, and demonstrated that non-clinical participants scoring high on Physical Anhedonia (a facet of Negative schizotypy) exhibited greater stress-induced deactivation of striatal and limbic regions compared to control participants and those scoring high on Perceptual Aberration (a facet of Positive schizotypy) [53]. Additionally, across all participants, Physical Anhedonia was correlated with stress-associated striatal deactivation [53]. Interestingly, as described in the *Neurochemistry* section, this same group observed in a separate study that participants scoring high for Physical Anhedonia exhibited greater stress-induced release of presynaptic dopamine, compared to controls and participants with high levels of Perceptual Aberrations [54].

Neurobiological Studies: Structural and Neurochemical Findings

Structural Neuroanatomy

Numerous studies have examined differences in the size of specific brain regions in SPD and schizotypy in comparison to healthy participants, patients with schizophrenia, and other personality disorders. A number of recent reviews have comprehensively discussed neuroanatomical findings in SPD, therefore, we will highlight overarching patterns and recent studies, here.

Temporal lobe—One of the most consistent findings in SPD has been temporal lobe volume reductions, possibly specific to the left hemisphere. Generally speaking, temporal lobe volume reductions in SPD are similar to those observed in studies of schizophrenia, but occur in a more restricted pattern [55-57]. Although not invariantly observed, reduced size of the left superior temporal gyrus (STG) has received significant attention [57;58]. However, the fusiform and middle temporal gyri have also been found to be reduced, but not the inferior temporal gyrus [56]. Recent studies have demonstrated that not only do the temporal lobe volume reductions in SPD occur in a more anatomically restricted manner than they do in in schizophrenia, but temporal lobe volume reductions appear to be progressive over time in schizophrenia, whereas in SPD they are relatively stable [56;57]. Generally speaking, involvement of the left temporal lobe suggests both auditory and language-related processes may be affected. Studies have demonstrated correlations between lower temporal lobe size with poorer logical memory [59], the odd speech SPD diagnostic criterion [58], and possibly, cognitive-perceptual symptoms [55].

Frontal lobe—Frontal lobe findings in SPD are of particular interest given the importance and recent focus on cognitive and working memory impairments in the schizophrenia-spectrum. However, unlike temporal lobe differences in SPD which have been relatively consistent between studies and similar although narrower in scope relative to those of schizophrenia, frontal lobe findings in SPD have been more variable. For example, we have demonstrated prefrontal cortex gray matter volume reduction in schizophrenia compared to both SPD patients and control participants; and no significant differences between the SPD and control groups. Moreover, we found volume differences of Brodmann's area (BA)10 -- a prefrontal region -- in SPD and schizophrenia were contradistinctive. In other words, BA10 was increased in SPD, compared to controls and patients with schizophrenia, and decreased in schizophrenia compared to controls and SPD patients. However, a recent study of neuroleptic-naïve men with SPD demonstrated widespread reductions in cortical gray matter volumes, including the frontal lobe; and no regions were identified with larger cortical volumes [60]. To complicate matters further, in studies of healthy, non-clinical participants those with high psychometric schizotypy demonstrated greater prefrontal [61] and global cortical gray matter volumes [62]. This has led to the hypothesis that general sparing of frontal lobe involvement in SPD, relative to that of schizophrenia, represents a ‘protective factor’ against the development of frank psychosis.

Striatum—In addition to cortical regions, such as the temporal and frontal lobes, structural and anatomical differences of the striatum have also been examined in patients with SPD. The striatum plays an essential role integrating cortical, thalamic and other subcortical processes in order to promote coherent sensori-motor, cognitive, and emotional/motivational function. While findings have been inconsistent, some general patterns have begun to emerge. Regions composing the associative striatum --most of the caudate and the pre-commissural putamen -- have generally been implicated. Initial reports from our group described smaller putamen volumes of patients with SPD compared to controls, whereas putamen size in patients with schizophrenia was relatively larger than that of control participants [63]. No differences of caudate volumes were observed, however. These findings suggested that smaller putamen volumes might reflect a compensatory change against pathogenesis of an overt psychotic syndrome. However, more recently, in a larger study of antipsychotic naïve SPD patients, we observed increased putamen volumes, specifically in the ventral and dorsal aspects [64]. Again, no differences in caudate volumes were observed. Interestingly, greater putamen size correlated with *less* severe paranoid symptoms. Therefore, it was proposed that increased putamen volumes in SPD patients may be a ‘protective’ factor against development of psychosis. Discrepancy with our earlier study was attributed to differences in sample size, gender ratios, medication history, or heterogeneity of the disorder. Nevertheless, larger putamen size in SPD patients was consistent with larger putamen volumes in schizophrenic patients with better outcomes (possibly reflecting therapeutic sensitivity to antipsychotics) compared to poor-outcome schizophrenia patients [65].

A separate group has also examined striatal neuroanatomy in patients with SPD, but have found abnormalities of caudate, rather than putamen, volume and morphology. They have consistently found smaller caudate volumes in SPD patients compared to control

participants. Moreover, they have found global and regional morphological abnormalities of the caudate nucleus in patients with SPD, most marked in the right caudate head. Generally speaking, these caudate volume differences correlated with cognitive impairments [37-39;66].

Other regions and Structural Connectivity—Structural abnormalities of the **cingulate gyrus**, a limbic cortical region that overlays the internal capsule and is involved in a range of cognitive/attentional and motivational/emotional functions, have also been described in SPD. We have previously observed reduced gray matter volumes in anterior cingulate posterior cingulate [55]. Findings in schizophrenia were similar to those of SPD patients, particular with respect to reduced BA31 volumes [55]. Furthermore, we have found that comorbidity of SPD in patients with BPD was associated with accentuated or additional gray matter loss of the posterior cingulate, compared to BPD patients without SPD [67]. However, not all studies have found volumetric differences in the anterior cingulate in SPD patients [68]. One group, however, has described that the right-greater-than-left asymmetry of the anterior cingulate observed in healthy female participants is absent among female patients with SPD [69].

Studies have also begun to examine **structural connectivity**, using diffusion tensor imaging (DTI), which can be used to assess fiber tract integrity [70]. In patients with SPD, lower fractional anisotropy (FA) of the uncinate fasciculus (UF), which is involved in fronto-temporal connectivity, was observed in SPD patients compared to healthy control participants [71]. However, no differences in the integrity of the cingulum bundle (CB), another important fiber tract bundle involved in connectivity of prefrontal, temporal, and parietal cortices, were observed between SPD patients and healthy control participants. Finally, lower left UF cross-sectional areas predicted poorer cognitive performance, whereas lower right UF areas were correlated with greater SPD Interpersonal symptomatology [71]. In accordance with these findings, FA of the right UF has also been shown to correlate with the personality trait, Extraversion, in patients with SPD but not in healthy control participants [72]. Our group recently examined the integrity of the anterior limb of the internal capsule (ALIC) which carries fibers between the thalamus and frontal lobe in patients with SPD. We found decreased volumes of the mid-ventral portion of the ALIC in SPD patients compared to controls; and, fewer fiber tracts in the dorsal portion of the ALIC terminating in BA10 but not BA45; and fewer dorsal-ALIC fibers correlated with greater severity of SPD symptomatology [73].

Dopamine Neurochemistry

Consistent with the role of the dopaminergic system in schizophrenia, studies have also begun to characterize dopamine neurochemistry in SPD using methods such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging. In an early study from our group [74], we used SPECT imaging to characterize striatal presynaptic dopamine release by examining the degree of amphetamine-induced displacement of the D2 receptor radioligand, [123I]IBZM: greater presynaptic dopamine releasing capacity is associated with greater decreases in [123I]IBZM binding after amphetamine challenge. No differences in striatal [123I]IBZM binding were observed

between SPD patients and healthy control participants, indicating no significant differences in striatal D2 receptor availability, itself, in SPD patients. However, post-amphetamine decreases in striatal [123I]IBZM binding SPD patients were almost twice that of healthy control participants, suggestive of relatively greater presynaptic dopamine release in SPD patients. Moreover, the degree of presynaptic dopamine release in SPD patients was similar to that observed in patients with remitted schizophrenia, but approximately half that of schizophrenic patients with an acute exacerbation of symptoms [74].

Further published studies have examined dopaminergic neurochemistry in healthy, non-clinical participants characterized with well validated self-report scales of schizotypy. Stress-induced striatal dopamine release, as indexed by comparing striatal [11C]raclopride binding during a control and mental arithmetic task, was shown to be elevated only in a group scoring high on a measure of negative schizotypy (Chapmann's Physical Anhedonia scale), but not in a group scoring high on a measure of positive schizotypy group (Chapmann's Perceptual Aberration scale) nor in a control group [54].

Examining amephtamine-induced changes in [11C]fallypride binding, the association between presynaptic dopamine release and schizotypal traits was examined in healthy participants assessed with the schizotypal personality questionnaire (SPQ) [75]. A positive correlation was found between total schizotypy, as measured by the SPQ, and striatal presynaptic dopamine release. This relationship was found to be primarily related to presynaptic dopamine release in the associative striatum and the *Disorganized* schizotypal traits [75]. Further exploratory analyses indicated a positive correlation between presynaptic dopamine release in a number of other cortical and subcortical regions [75]. In a separate study, *Disorganized* traits, in non-clinical adults assessed with the SPQ, were positively correlated with D2 dopamine receptor availability, as measured by SPECT imaging with [123I]IBZM binding, in the right striatum [76]. Lastly, dopamine synthesis capacity in a non-clinical group with subclinical auditory hallucinatory phenomena did not differ from a control group; and schizotypal and other psychosis-spectrum symptoms were not related to dopamine synthesis capacity [77].

Unpublished preliminary studies from our group have examined striatal dopamine release using amphetamine-induced [11C]raclopride displacement. These studies suggested greater presynaptic dopamine release, but specifically, in SPD patients under 40 years of age. Further, presynaptic dopamine release in SPD patients under 40 years old, appeared to be positively correlated with cognitive-perceptual (or positive) symptoms and enhanced working memory performance. Presynaptic striatal dopamine, on the other hand, appeared to be inversely correlated with negative symptoms, such as Interpersonal symptoms and social anhedonia in the under-40 SPD patients.

Clinical Perspectives

Identifying SPD and associated traits in the clinical setting can be challenging as manifestations overlap with many other more well-known psychiatric conditions, or may simply be qualified in colloquial terms (e.g., loner) without further diagnostic attribution. Common complaints of patients with SPD or schizotypal traits are related to attentional/

cognitive difficulties, social anxiety, difficulty “connecting” to others, and longstanding interpersonal complications related to suspiciousness/paranoia. Superficially healthier SPD patients may present with characteristic anxieties or ‘neurotic conflicts’ that are, in a more latent manner, determined or exacerbated by underlying magical ideation, odd beliefs, or overvalued ideas.

Therefore, schizotypal patients are not uncommonly diagnosed with attention-deficit disorder (inattentive type); social anxiety disorder; autism-spectrum; dysthymia. Additionally, the role of an underlying odd/magical belief as an aggravating factor of a concurrent symptom disorder (e.g., anorexia, OCD) may be overlooked. what appears anxiety-related complaints or other symptom disorders can be overlooked. Additionally, many of the cognitive/perceptual disturbances that schizotypal patients can bring to a clinician's attention can be quite dramatic or alarming, and even though these phenomena are not associated with patient has a fair degree of intact reality testing, patients may nevertheless receive a diagnosis of a formal psychotic illness. Clinically significant schizotypy can exacerbate the treatment of other clinical syndromes that may be the primary area of focus. For example, schizotypy has been shown to be a potential negative prognostic factor in OCD. We have found that the underlying core beliefs associated with certain disorders can have a more concrete quality or be relatively refractory to insight.

Medications can play either a primary or adjunctive role in treatment of patients with SPD or schizotypal traits. Importantly, however, clinical trials for SPD or specific schizotypal symptoms are rare, and therefore, our recommendations are based on our clinical experience and discussions with colleagues. We have found that attentional and cognitive difficulties are responsive to stimulants, such as those used to treat attention deficit disorder. Although the use of stimulants in those with a vulnerability to psychosis certainly requires close clinical monitoring, we have not found stimulant use in SPD patients to be problematic in this regard. On the contrary, we find that the enhanced cognitive function may limit stress-induced impairment of executive function, and therefore, lessen the propensity more regressive forms of thought processes. Moreover, mood and social anxiety symptoms can also be alleviated during a course of stimulant treatment, however, we do not recommend their use for indications other than attentional or cognitive difficulties. Early evidence from our group also supports a possible role for guanfacine, which also has an indication for attention-deficit disorder [35]. We did not observe any benefit of the atypical antipsychotic, risperidone, on cognitive function in patients with SPD. Risperidone (0.25-2 mg), however, has been shown to improve both positive and negative symptomatology in patients with SPD [78]. Antipsychotics should be used judiciously in SPD patients, especially since these symptoms are not necessarily the most disturbing to patients, nor are they necessarily the most problematic. Antipsychotics certainly play an important role when SPD patients develop brief psychotic episodes, which they are susceptible to during periods of elevated psychosocial stress. We have also found that benzodiazepines can play in important role in the treatment of anxiety in SPD, however, it is not uncommon that symptoms may only be partially relieved. In contrast to the treatment of generalized anxiety, social anxiety, and panic disorder, we have not been impressed with the effectiveness of serotonin reuptake inhibitors (SRIs) on SPD-associated anxiety. Moreover, we have not found antidepressants to be particularly effective for the dysthymic and anhedonic symptoms of SPD.

The literature on psychotherapy for patients with SPD is close to non-existent. Stone's manuscript of his clinical experience treating schizotypal patients psychotherapeutically, although close to 30 years old, remains highly relevant [79]. Psychotherapy with SPD patients can be limited by a variety of possible interpersonal complications. On the one hand, paranoia and limited capacity/desire to form close personal relationships can be a barrier for developing a therapeutic alliance. On the other hand, in SPD patients with the capacity and desire to form relationships, complications can arise during periods of treatment intensification and separation. Patients with SPD may experience a blurring of the boundaries between themselves and the therapist as treatment advances. For example, a high functioning SPD patient in psychotherapy began expressing a feeling that she and the therapist ‘knew each other from someplace else’ after the therapist had linked the patients symptomatic, excessive conscientiousness with her description of her siblings as being unreliable during childhood. This was taken as an indication to the therapist that this standard psychotherapeutic intervention may not have suitable at that time. Additionally, SPD patients may either be unable to tolerate regular or extended periods of separation; alternatively, they may have difficulty experiencing continuity between sessions -- as if the work of each session wasn't cumulative, but rather, was just another “new” session.

Peculiarities of thought and semantic processing make it very difficult for SPD patients to be understood and/or communicate complex emotional and psychological states and concepts that are typically required in psychotherapy. Furthermore, SPD patients can have a limited capacity to think about their mental states abstractly; or, they may find the process to be disconcerting or destabilizing. We have also noted that SPD patients exhibit a striking capacity for disavowal of certain realities, which further complicates the process of psychotherapy as the anxiety associated with certain external consequences plays less of a motivating role for psychological change.

Vivid perceptual/dissociative disturbances that are associated with elaborate magical beliefs require a delicate psychotherapeutic approach, as SPD patients can simultaneously (albeit in an unintegrated manner) recognize these thoughts and experiences as symptoms, yet at the same time, ascribe them to reality. Therefore, a challenge for the psychotherapist is to be able to tolerate and help the patient tolerate these complicated and troubling experiences.

Lastly, there is significant individual variability in terms of what types of psychotherapeutic interventions SPD patients could benefit from; and, ultimately, this can only be assessed empirically during the initial and extended evaluation process. Therefore, once clinically significant schizotypy has been identified, this should prompt the clinician to pay particularly close attention to various factors, such as: the ability of the patient to form a therapeutic alliance; the patient's expectation of what are reasonable psychotherapeutic goals, and psychotherapy is supposed to work.

Conclusions

SPD is significant both as a clinical syndrome and, from a research perspective, as an intermediate schizophrenia-spectrum phenotype. From a clinical standpoint, SPD is relatively understudied, compared to other personality disorders, and a great deal needs to be

understood with respect to both pharmacological and psychotherapeutic interventions. SPD can be challenging to identify, as diagnostic phenomena may be a) difficult to elicit, b) attributed to more familiar diagnoses, or c) go unrecognized. Other important phenomena, namely, cognitive deficits (attentional, executive function, and working memory impairments), may not lead one to consider a diagnosis of SPD as they are not formally represented in the DSM diagnostic criteria. Nevertheless, such cognitive impairments are strongly associated with SPD and play an important role in determining functional outcomes. Recognition of SPD may be aided by appreciation of its multidimensional nature, typically represented in terms of *Cognitive-Perceptual*, *Oddness/Disorganized*, and *Interpersonal/Negative* domains. SPD is a heritable condition, consisting of both genetic and environmental factors (e.g., psychological trauma). There are factors that contribute to the development of SPD itself, as well as its component domains (e.g., *Cognitive-Perceptual*). In terms of the neurobiology of SPD, there are shared and divergent elements with respect to schizophrenia. For example, both SPD and schizophrenia exhibit decreased left temporal lobe volumes; however, in SPD, temporal lobe volume abnormalities are anatomically more circumscribed, and less progressive over time than in schizophrenia. Frontal lobe and striatal anatomical abnormalities have also been identified in SPD; however, these findings have been less consistent, and may also consist of compensatory or ‘protective’ factors that limit progression to full psychosis. Dopaminergic neurochemistry in striatal and cortical regions appears to play an important role in SPD and schizotypal traits in non-clinical participants. Areas in need of future focus include characterization of schizotypy in child and adolescent populations, including further understanding of relationship with autism-spectrum conditions; studies on psychopharmacological and psychotherapeutic treatments; characterizing neural correlates and therapeutics of cognitive impairment.

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