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White matter alterations in individuals experiencing attenuated positive psychotic symptoms

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Abstract

Objective—Diffusion tensor imaging (DTI) studies suggest that reduced fractional anisotropy (FA) in the inferior longitudinal fasciculus (ILF) and superior longitudinal fasciculus (SLF) occurs among schizophrenia patients and those at risk for psychosis. Nevertheless, there is a dearth of knowledge investigating white matter fiber pathways in non-help seeking individuals who endorse attenuated positive psychotic symptoms (APPS) across a range of mental disorders. The aim of the current study was to determine if alterations in ILF and SLF microstructure were specific to distressing APPS related to risk for psychosis or to APPS symptoms occurring in multiple mental disorders, which would suggest a shared phenotype among disorders.

Method—Twenty-six non-help seeking young adults were administered the Prodromal Questionnaire. DTI was conducted on participants (n = 13) who endorsed 8 or more distressing APPS (D-APPS, a potentially clinically relevant group) and those who endorsed 3 or fewer distressing APPS (low-APPS; n = 13). Semi-structured interviews were administered to determine diagnoses, as well as clinical risk for psychosis status.

Results—Results indicated that the D-APPS group exhibited decreased FA in the left ILF compared with the low-APPS group, even after removing 4 D-APPS participants who were considered at risk for psychosis.

Discussion—Findings suggest that white matter microstructure is altered in individuals experiencing APPS across a range of disorders, independent of clinical high risk for psychosis status. Reduced FA in the left ILF may not be specific to psychosis risk, but rather for APPS that occur in a number of mental disorders.

Keywords

attenuated positive psychotic symptoms; DTI; psychosis; schizophrenia; white matter

INTRODUCTION

Recently, structural connectivity analyses have become a popular technique for examining potential differences in connectivity profiles and properties across various clinical populations. One such technique, diffusion tensor imaging (DTI), specifically measures the

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degree and direction of diffusion of water molecules within human brain tissue. Structural connections, or white matter tracts, are made up of myelinated axons in which the direction of diffusion is restricted due to the presence of myelin sheaths. DTI indexes this degree of this restriction, called anisotropy.[1] DTI studies have demonstrated that individuals with chronic schizophrenia have altered white matter connectivity throughout the brain.[2,3] Similarly, those experiencing first episode psychosis exhibit widespread white matter disruption across many tracts including callosal pathways, limbic tracts, and association tracts (e.g., the superior longitudinal fasciculus (SLF) and the inferior longitudinal fasciculus (ILF))., reducing the possibility that findings are secondary to prolonged medication use.[4–9] Moreover, reduced fractional anisotropy (FA) in the ILF has been linked to increases in scores on the Positive and Negative Syndrome Scale, suggesting that it may have relevance to psychotic symptomology.[4,10] Additionally, reduced FA in the SLF has been implicated in the language and cognitive functioning seen in psychosis spectrum disorders.[11]

White matter abnormalities have also been found prior to the onset of psychosis and in those experiencing subthreshold psychotic symptoms.[2,12–15] Across studies, white matter differences were most consistently observed in the SLF and ILF in populations deemed at clinical high risk for psychosis (CHR)[14] and in the inferior fronto-occipital fasciculus, cingulum bundle, and ILF in children experiencing subthreshold psychotic symptoms.[15] Studies show that the ILF appears to be specifically associated with symptomatology in CHR[13,16], whereas the SLF has been associated with functional and cognitive deficits in CHR populations, but not with symptomatology.[17]

Nevertheless, it remains unclear whether these white matter aberrations are specific to psychotic disorders and those at CHR for psychosis or whether these white matter disruptions are specific to attenuated positive psychotic symptoms (APPS; symptoms that do not reach fully psychotic criteria) that occur in the context of a range of mental disorders. The preponderance of studies have examined APPS as occurring in those at risk for psychosis; however, APPS occur in a number of mental disorders (e.g., depression, post-traumatic stress disorder, and anxiety disorders)[18,19], as well as in individuals without diagnosed mental health disorders.[20] Epidemiological studies have assessed non-clinical samples experiencing APPS and have found that 18%–28% of individuals report psychotic-like experiences.[21,22] While the method of measurement used in a given study results in varying numbers, the prevalence of psychotic disorders are always much lower than the percentage of individuals endorsing psychotic-like symptoms.[22] It is therefore unclear whether brain abnormalities found in previous studies are specific to risk for psychosis or whether these brain abnormalities are specific to an APPS phenotype that can occur across a range of disorders.

The present study investigated whether there were differences in white matter microstructure in individuals experiencing 8 or more distressing APPS (D-APPS) relative to those experiencing few APPS (low-APPS; a control comparison group). The comparison groups were specifically chosen to represent individuals who varied on APPS, but exhibited a range of mental disorders. Analyses also were conducted when including and excluding individuals at CHR for psychosis to determine whether findings were specific for an APPS phenotype that crosses multiple mental disorders and not to CHR for psychosis. Based on

prior findings in CHR populations[14], we focused on two commonly implicated tracts: the SLF and the ILF. Given research linking reduced FA in the ILF, but not the SLF, to positive symptoms and CHR status, we hypothesized that reduced FA in the ILF and not in the SLF would be associated with D-APPS across a range of mental disorders in a non-help seeking population.[14]

METHOD

All methods were approved by the Temple University Institutional Review Board.

Participants

Participants (N = 27) were recruited via the university's online subject pool. Individuals whose scores on the Prodromal Questionnaire (PQ)[23] placed them into the D-APPS (n = 14) or low-APPS (n = 13) groupings were invited to participate in the imaging and clinical interview components of the study. Participants were given course credit for completing questionnaires and compensated a nominal fee for their time for participating in imaging and the interview.

Participants were at least 18 years of age, right-handed, and recruited from an undergraduate sample. Our sample size for analyses was reduced to 26 cases due to unusable imaging acquisition for one participant in the D-APPS group; samples for analyses consisted of 13 D-APPS individuals and 13 low-APPS individuals. No significant differences between groups emerged for age or gender. See Table 1 for participant demographic characteristics.

Procedures

Instruments—APPS were evaluated using the positive symptom subscale (45 items) of the full length, 92-item Prodromal Questionnaire (PQ)[23], which has established validity in identifying individuals who are at risk for a psychotic disorder. As previously described in the literature[24], items endorsed were rated as to whether or not they were distressing by the participant. The current study used the positive symptoms subscale scores and summed the presence or absence of endorsed symptoms (45 items total). Group membership was determined by endorsement of eight or more distressing APPS (D-APPS group) compared to three or fewer distressing APPS (low-APPS group; the mean of APPS distressing symptoms in our larger undergraduate sample[24,25]). Endorsing eight or more distressing APPS has achieved 90% sensitivity and 49% specificity in correctly classifying CHR for psychosis cases identified using the Structured Interview for Psychosis-Risk Syndromes (see below) in clinical samples[20], and 2% of an undergraduate sample met this criterion[23,26], which generally corresponds to expected lifetime prevalence rates of psychotic disorders in the general public.[27]

The Structured Interview for Psychosis-Risk Syndromes (SIPS) was used to identify the presence and severity of psychosis-risk syndromes, which is a widely-used, well-validated clinical interview to identify individuals who meet criteria for a psychosis-risk syndrome.[28] Individuals who meet criteria for one of these syndromes have between a 30–43% chance of developing psychosis within 2.5 years.[29,30]

The Structured Clinical Interview for the DSM-IV (SCID)[31] was conducted with all participants to rule out clinical level psychotic disorders and to determine mental disorders in both the D-APPS and the low-APPS groups. Advanced graduate students who were blind to participants' PQ status conducted the interviews after extensive training and reliability of kappa >.80 on scored clinical videos. Interviews were reviewed in consensus review meetings with L.M. Ellman and at least three trained diagnosticians.

Imaging—Magnetic resonance imaging (MRI) was conducted at Temple University Hospital on a 3.0 Tesla Siemens Verio scanner (Erlangen, Germany) using a Siemens twelve-channel phased-array head coil. DTI data were collected using a diffusion weighted echo-planar imaging (EPI) sequence covering the whole brain. Salient imaging parameters were as follows: 30 axial slices, 4 mm slice thickness, TR = 4,300 ms, TE = 95 ms, FOV = 240 mm^2, b values of 0 and 1000 s/mm^2, 20 non-collinear directions.

The diffusion-weighted data were pre-processed using FSL[32] to correct for eddy currents and subject motion using an affine registration model. The b-vector matrix was adjusted based on rigid body registration, ensuring a valid computation of the tensor variables. Non-brain tissue was removed using FSL's[32] automated brain extraction tool (BET), and a standard diffusion tensor fitting model was then applied to the data. The diffusion tensor fitting provided estimates of FA, as well as three eigenvectors and eigenvalues. These estimates were computed on individual voxels using a three-dimensional Gaussian distribution model that yielded a single mean ellipsoid for each voxel.

Data Analysis

Tract-based spatial statistical analyses—Voxel-wise statistical analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS[33]) in FSL.[32] TBSS is an approach previously used in schizophrenia samples, and has become standard in DTI research.[34] All participants' FA data were aligned to MNI152 standard space by using the nonlinear registration tool FNIRT.[35] First, each participant's FA image was aligned to every other participant's FA image in order to find the most representative image. The most representative image was then used as a target image and was affine-aligned into MNI152 space. Next, participants' FA data were transformed by combining the nonlinear transform to the target FA image with the affine-aligned transform from the target image into MNI152 space. Then, a mean FA image was created and thinned to construct an FA skeleton that represents the centers of all tracts common to the group. Finally, the aligned participant FA data was projected onto this skeleton to be used for further data analysis. White matter tract masks from the Johns Hopkins University white matter tractography atlas[36,37] were used to localize the SLF and ILF. These masks were projected onto the skeletonised FA data in order to extract mean FA values of bilateral SLF and ILF for each participant.

Statistical analyses—Statistical analyses were performed using SPSS (Version 21.0; IBM). To examine the relationship of FA values by group, independent *t*-tests were computed comparing the low-APPS group and D-APPS group, the latter when including and excluding those at CHR for psychosis. Prior to analyses, FA values were confirmed as normally distributed across the sample and within groups. We ran follow-up analyses to

examine additional DTI indices, including axial diffusivity, mean diffusivity, and radial diffusivity. No significant relationships were found. These data are presented in the supplemental material.

RESULTS

There were no significant differences in demographic characteristics or number of lifetime DSM-IV diagnoses between comparison groups, and participants in both groups presented with a wide array of mental disorders (see Table 1).

A within-samples *t*-test for each group indicated that there were significant hemispheric differences in the ILF for both the D-APPS group [$t(12) = 4.306$, $p = .001$] and the low-APPS group [$t(12) = 2.419$, $p = .032$], so hemispheres were analyzed separately. An independent-samples *t*-test revealed that FA values in the right ILF did not differ between groups [$t(24) = 1.273$, $p = .215$]; however, mean left ILF FA was significantly lower in the D-APPS group, compared to the low-APPS group, $t(24) = -2.228$, $p = 0.036$ (see Figures 1 & 2). FA values in the left ILF remained significantly lower in the D-APPS group, relative to the low-APPS group, even after removing four individuals at CHR for psychosis, $t(20) = -2.276$, $p = 0.034$ (see Figure 2).

A within-samples *t*-test for each group indicated that there were significant hemisphere differences in the SLF for the low-APPS group [$t(12) = 3.396$, $p = .005$], but not for the D-APPS group [$t(12) = 0.118$, $p = .908$]. Nonetheless, to keep analyses consistent, hemispheres were analyzed separately. An independent-samples *t*-test indicated that FA values in neither the left SLF [$t(24) = 0.864$, $p = .396$] nor the right SLF [$t(24) = -0.736$, $p = .469$] were significantly different between the D-APPS group and the low-APPS group (See Figure 2).

DISCUSSION

To our knowledge, this is the first study to determine that reduced FA in the left ILF (white matter microstructure alteration, in general) is associated with experience of distressing APPS across a range of mental disorders, irrespective of CHR for psychosis status. These results are consistent with both the psychosis and non-help seeking APPS literatures, which have shown alterations in white matter across the schizophrenia spectrum, from children experiencing subthreshold psychotic symptoms to those at CHR for psychosis to chronic patients.. When the four D-APPS individuals determined to be at CHR risk for psychosis (as measured by the SIPS interview) were removed from the sample, reduced FA in the left ILF remained significant, indicating that variability in the left ILF may be more related to the APPS phenotype across a range of mental disorders than to psychosis risk and/or psychotic disorders. Due to the small number of CHR individuals in the current study, comparing white matter differences in CHR relative to non-CHR individuals was not possible; however, the findings from the present study are consistent with previous DTI studies of CHR populations.[2,13,14] Further, there was no difference in the total number of mental disorders between D-APPS and low-APPS groups, indicating that white matter variations were primarily associated with differences in experience of distressing APPS (as measured by questionnaire and confirmed with semi-structured interviews), the key phenotype that

appeared to differentiate the two study groups. The finding is especially important as it suggests that aberrations in white matter microstructure may represent a shared phenotype among related disorders rather than a brain abnormality specific to psychotic disorders, and therefore has implications for research efforts aimed at determining the causes of psychotic disorders more generally.

The general function of association white matter pathways is to reciprocally connect gray matter loci in order to establish neural networks that facilitate the transmission of information.[38] Thus, the functionality of white matter is closely associated with the gray matter loci from which it is derived. The ILF connects extrastriate visual areas to limbic regions, including the amygdala and the anterior and medial temporal lobes[39], which suggests that that the ILF is involved in linking visual perception to memory and emotion. Unger and colleagues (In Press) reported that individual differences in ILF microstructure predicted one's ability to discern emotional faces, a deficit frequently noted in psychosis populations.[40–42] Moreover, focal damage to the ILF has been associated with hypoemotionality to visual stimuli, such that visual stimuli that are typically emotionally evocative fail to produce any effect, either positive or negative.[43] Interestingly, one study reported that in schizophrenia, disruptions in ILF microstructure correlated with the presence of visual hallucinations.[44] Other studies in the schizophrenia literature have reported associations between the ILF and thought disorder[45], cognitive impairments such as verbal and visual learning[46], and deteriorating social and role functioning in CHR but not in non-CHR individuals.[47] The current findings suggest that reduced FA in the ILF may represent microstructural aberrations that underlie a shared phenotype between multiple disorders, rather than a brain abnormality specifically limited to psychosis.

Strengths of this study include the use of a non-help seeking population. Our comparison group endorsed mental health disorders as well as APPS, which strengthened our study as it allowed us to focus on differences in white matter as they relate to the experience of APPS. Had our comparison group not experienced similar rates and types of mental disorders, differences that emerged may have been due to overall mental health.[48] Further, the prevalence rates of mental disorders in our control group were similar to those reported in college populations, with evidence suggesting that about half of all college students have met criteria for at least one DSM-IV diagnosis in the past year and that rates of mental health disorders are increasing among college students[49]. Another strength of the present study was that data were collected by self-report and confirmed by clinical interview. Limitations of the study are that the sample was small and comprised mostly of females. No statistical gender differences, however, emerged between groups. Regardless, analyses were rerun through analysis of covariance (ANCOVA) tests while controlling for gender, and the results were consistent. Additionally, it is unclear whether some of the D-APPS individuals will develop psychotic disorders, even though CHR for psychosis was excluded in secondary analyses. Future studies should seek to build upon these findings using a larger and more gender-balanced sample, including additional comparison groups (e.g., non-psychiatric controls and CHR for psychosis), and follow up evaluations to determine long-term clinical outcomes. Finally, future longitudinal studies should compare white matter connectivity among individuals experiencing D-APPS across a range of mental disorders to investigate potential additional white matter disruptions across time (e.g., upon conversion to

schizophrenia) and/or progression of symptoms (e,g, for schizophrenia and other mental health disorders).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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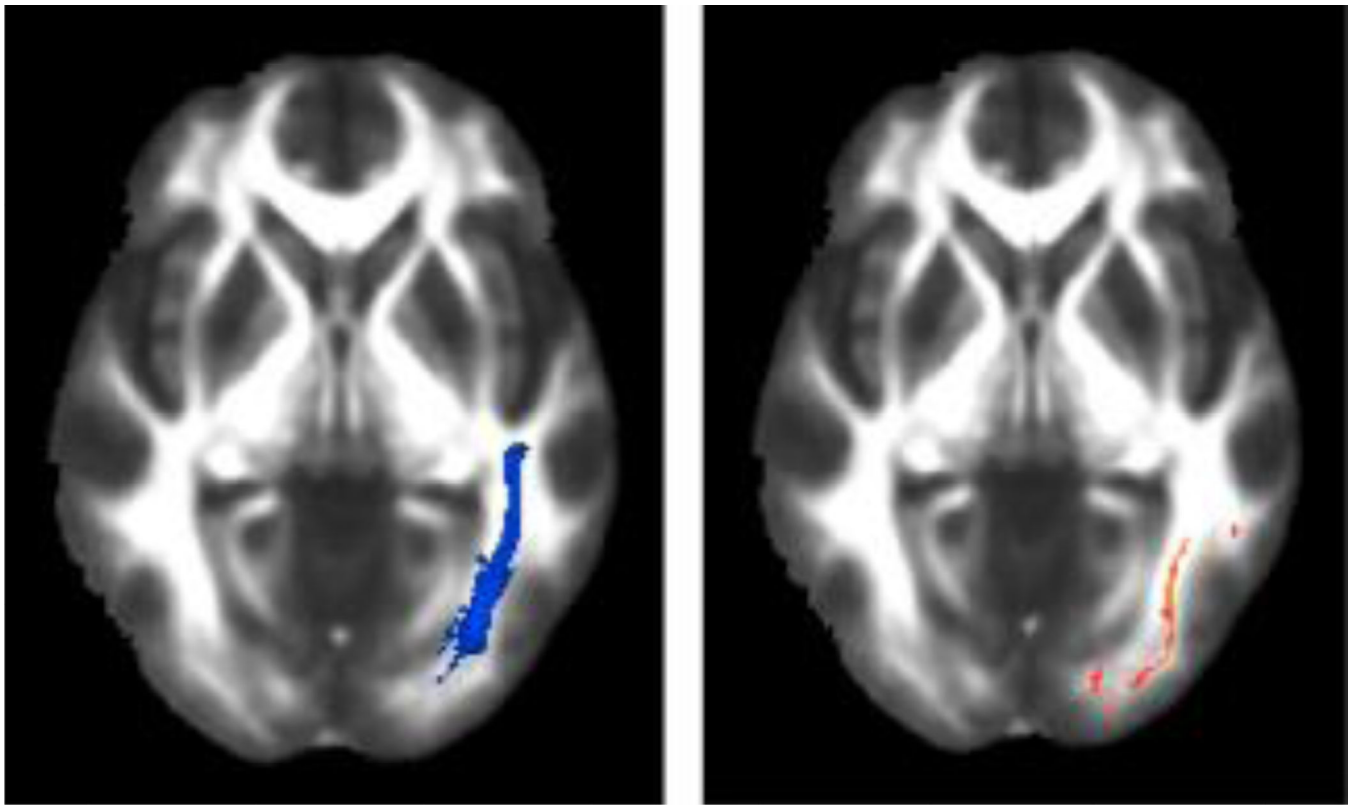

Figure 1. White matter alterations in individuals experiencing attenuated positive psychotic symptoms

Left image: Image of the left inferior long fasciculus. Right image: Higher fractional anisotropy values in individuals experiencing 3 or fewer distressing attenuated positive psychotic symptoms (Low-APPS) as compared to individuals experiencing 8 or more distressing attenuated positive psychotic symptoms (D-APPS).

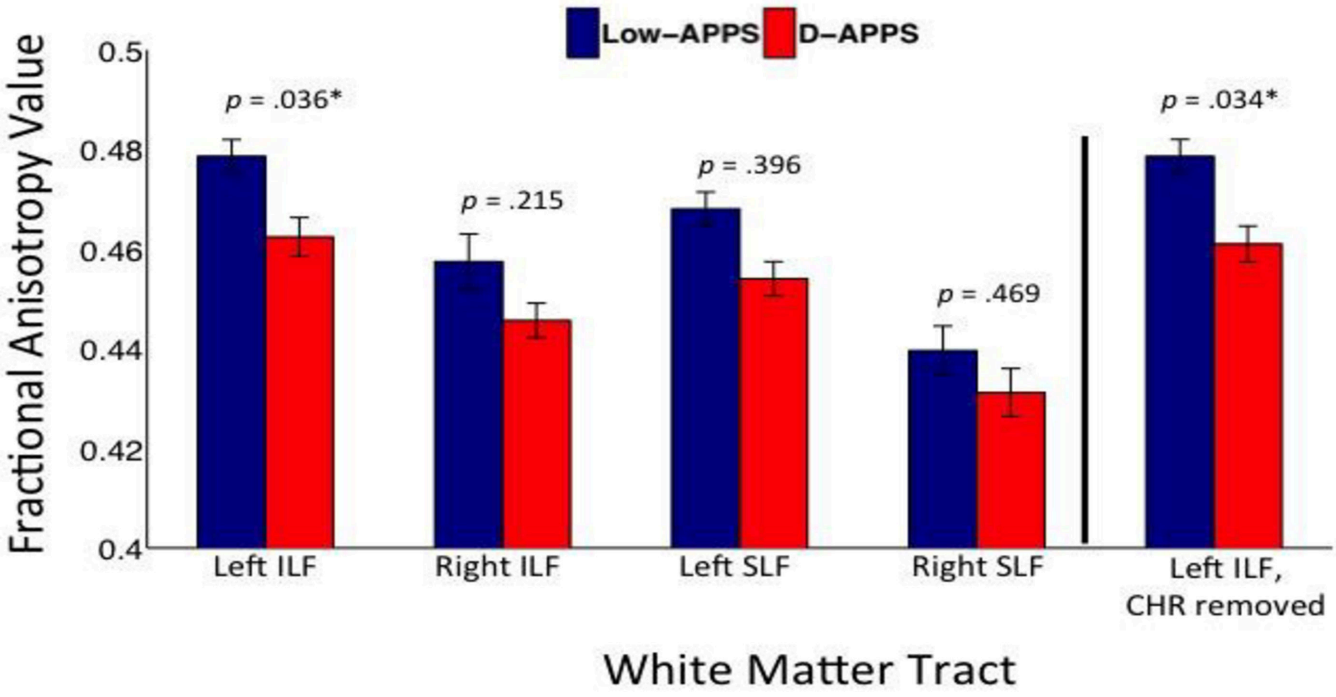

Figure 2. Fractional anisotropy values in white matter tracts of interest for individuals with and without attenuated positive psychotic symptoms

Table 1

Participant Characteristics.

	D-APPS (*n*=13)	Low-APPS (*n*=13)	*p*-value
Gender: F%	69.20	76.90	.052
Age: mean (SD) [range]	20.75 (2.60) [17–27]	20.00 (1.81) [18–23]	.421
Race/Ethnicity: # (%)			0.69
White	9 (69.20)	7 (53.80)	-
Black	1 (7.70)	1 (7.70)	-
Other	3 (23.10)	5 (38.50)	-
APPS (PQ): mean (SD) [range]	20.50 (7.13) [9–31]	4.39 (2.40) [0–8]	<.001***
CHR	23.50 (5.86)	-	
non-CHR	18.13 (7.36)	-	
APPS-Distressing (PQ): mean (SD) [range]	12.64 (6.25) [8–27]	1.62 (1.33) [0–3]	<.001***
CHR	14.75 (1.53)	-	
non-CHR	12.38 (5.97)	-	
CHR (SIPS): *N* (%)	3 (23.08)	0 (0)	
Positive Psychotic Symptomatology (SIPS): (endorsing ≥ 3 items)			
Unusual Thought Content/Delusional Ideas	3	0	
CHR	2	-	
non-CHR	1	-	
Suspiciousness/Persecutory Ideas	7	0	
CHR	3	-	
non-CHR	4	-	
Grandiose Ideas	0	0	
CHR	0	-	
non-CHR	0	-	
Perceptual Abnormalities	3	0	
CHR	3	-	
non-CHR	0	-	
Disorganized Communication	1	0	
CHR	1	-	
non-CHR	0	-	
SCID: Lifetime Diagnoses (*f*)			
Major Depressive Disorder	10	6	
Post-Traumatic Stress Disorder	3	2	
Bipolar Disorder I	1	0	
Generalized Anxiety Disorder	4	1	
Social Anxiety Disorder	5	2	
Substance Abuse/Dependence	7	8	
Specific Phobia	3	2	
Panic Disorder	2	1	
SCID: Total Diagnoses (*f*)	35	22	0.09

APPS = attenuated positive psychotic symptoms, D-APPS = individuals who endorsed 8 or more distressing APPS; Low-APPS = individuals who endorsed 3 or fewer distressing APPS, and fewer than 8 total APPS; CHR = Clinical High Risk; SIPS = Structured Interview for Psychosis Risk Syndromes; SIPS: SCID = Structured Clinical Interview for the DSM-IV; *f* = frequency.