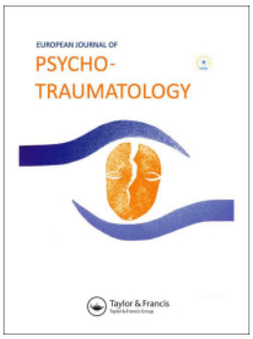

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CLINICAL RESEARCH ARTICLE

Attenuated psychotic symptoms, substance use and self-reported PTSD in adolescence

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ABSTRACT

Background: The occurrence of attenuated psychotic symptoms (APS) is a major concern in populations with substance use disorders (SUDs). However, APS also frequently develop in the course of Post-Traumatic Stress Disorder (PTSD). This study explores how the prevalence of APS differs between adolescent patients with only SUD, SUD with a history of traumatic experiences (TEs), and with SUD and self-reported PTSD.

Methods: We recruited $n = 120$ treatment-seeking adolescents at a German outpatient clinic for adolescents with SUD. All participants filled out questionnaires assessing APS (PQ-16, YSR schizoid scale), trauma history, PTSD symptoms (both UCLA PTSD Index), and SUD severity (DUDIT) next to an extensive substance use interview. We performed a multivariate analysis of co-variance with the four PQ-16 scales and the YSR scale as outcomes and PTSD status as predictor. Additionally, we performed five linear regressions predicting each PQ-16 score and YSR score based on tobacco, alcohol, cannabis, ecstasy, amphetamine, and methamphetamine use.

Results: Participants with co-occurring SUD and self-reported PTSD showed significantly higher APS prevalence rates (PQ-16 score, $p = .00002$), more disturbed thought content ($p = .000004$), more perceptual disturbances ($p = .002$), more negative symptoms ($p = .004$) and more thought problems ($p = .001$) compared to adolescents with SUD and a history of trauma and adolescents with only SUD. Past-year substance use was not predictive for APS prevalence ($F(75) = 0.42$; $p = .86$; $R^2 = .04$).

Conclusion: Our data suggests that the occurrence of APS in adolescents with SUD is better explained by co-occurring self-reported PTSD than by substance use frequency or substance class. This finding might indicate that APS might be reduced through treating PTSD or focusing on TEs in SUD therapy.

Síntomas psicóticos atenuados, consumo de sustancias y TEPT autodeclarado en la adolescencia

Antecedentes: La aparición de síntomas psicóticos atenuados (APS por sus siglas en inglés) es una preocupación importante en poblaciones con trastornos por uso de sustancias (SUD por sus siglas en ingles). Sin embargo, los APS también se desarrollan con frecuencia en el curso del Trastorno de Estrés Postraumático (TEPT). Este estudio explora cómo la prevalencia de APS difiere entre pacientes adolescentes con sólo SUD, SUD con una historia de experiencias traumáticas (TEs), y con SUD y TEPT autoinformado.

Métodos: Reclutamos $n = 120$ adolescentes que buscaban tratamiento en una clínica ambulatoria alemana para adolescentes con SUD. Todos los participantes rellenaron cuestionarios que evaluaban APS (PQ-16, escala esquizoide YSR), historia de traumas, síntomas de TEPT (ambos el Índice de TEPT de la UCLA) y la gravedad de la SUD (DUDIT) junto a una extensa entrevista sobre consumo de sustancias. Realizamos un análisis multivariante de covarianza con las cuatro escalas PQ-16 y la escala YSR como resultados y el estado de TEPT como predictor. Además, realizamos cinco regresiones lineales prediciendo cada puntuación PQ-16 y la puntuación YSR en función del consumo de tabaco, alcohol, cannabis, éxtasis, anfetaminas y metanfetaminas.

Resultados: Los participantes con SUD concurrente y TEPT autoinformado mostraron tasas de prevalencia de APS significativamente más altas (puntuación PQ-16, $p = .00002$), un contenido de pensamiento más perturbado ($p = .000004$), más alteraciones perceptivas ($p = .002$), más síntomas negativos ($p = .004$) y más problemas del pensamiento ($p = .001$) en comparación con los adolescentes con SUD y antecedentes de trauma y los adolescentes con sólo SUD. El consumo de sustancias durante el año anterior no fue predictivo de la prevalencia de APS ($F(75) = 0,42$; $p = 0,86$; $R^2 = 0,04$).

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Addiction; trauma; psychosis; drug use; adolescent

PALABRAS CLAVE
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关键词
成瘾; 创伤; 精神病; 药物使用; 青少年

HIGHLIGHTS

- Adolescents with co-occurring substance use disorders and PTSD show increased rates of Attenuated Psychotic Symptoms (APS).
- A history of traumatic experiences and PTSD are stronger predictors for APS than substance use.
- APS in adolescents with substance use disorders may be an indication of undiagnosed and/or untreated co-occurring PTSD.

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Conclusiones: Nuestros datos sugieren que la aparición de APS en adolescentes con SUD se explica mejor por el TEPT autoinformado co-ocurrente que por la frecuencia de uso de sustancias o la clase de sustancia. Este hallazgo podría indicar que los APS podría reducirse mediante el tratamiento del TEPT o centrándose en los TE en la terapia del SUD.

青少年中轻微的精神病症状、物质使用和自我报告的 PTSD

背景：轻微精神病症状 (APS) 的发生是物质使用障碍 (SUD) 人群的主要关注点。 然而，APS 也经常在创伤后应激障碍 (PTSD) 的过程中发展。 本研究探讨了 APS 的患病率在仅患有 SUD、有创伤经历 (TE) 史的 SUD 以及患有 SUD 和自我报告的 PTSD 的青少年患者之间有何不同。
方法：我们在德国 SUD 青少年门诊招募了120 名寻求治疗的青少年。 所有参与者都在广泛性物质使用访谈后填写了评估 APS（PQ-16，YSR 分裂样量表）、创伤史和PTSD 症状（均使用UCLA PTSD 指数）和 SUD 严重程度 (DUDIT) 的问卷。 我们用四个 PQ-16 量表和 YSR 量表作为结果，PTSD 状态作为预测因子，进行了协方差的多变量分析。 此外，我们根据烟草、酒精、大麻、摇头丸、苯丙胺和甲基苯丙胺的使用情况，进行了五项线性回归预测每个 PQ-16 评分和 YSR 评分。
结果：同时患有 SUD 和自我报告的 PTSD 的参与者相较于患有 SUD 且有创伤史的青少年和仅患有 SUD 的青少年，表现出显著更高的 APS 患病率（PQ-16 评分，$p = .00002$）、更不安的思想内容（$p = .000004$）、更多的知觉障碍（$p = .002$），更多的阴性症状 ($p = .004$) 和更多的思维问题 ($p = .001$)。 过去一年的物质使用不能预测 APS 患病率 ($F(75) = 0.42$；$p = .86$；$R^2 = .04$)。
结论：我们的数据表明，与物质使用频率或物质类别相比，同时发生的自我报告的 PTSD 可以更好地解释患有 SUD 的青少年 APS 的发生。 这一发现可能表明通过治疗 PTSD 或在 SUD 治疗中关注 TE 可能会降低 APS。

Trial registration: ClinicalTrials.gov identifier: NCT03444974.

1. Background

Early identification of individuals with an increased risk for psychotic disorders is one of the most important prerequisites for their efficient prevention and treatment. Attenuated psychotic syndrome (American Psychiatric Association & American Psychiatric Association, 2013) also known as attenuated psychotic symptoms (APS) are strong indicators of a patient being at ultra-high risk of developing psychosis (Fusar-Poli et al., 2013, 2016). APS refers to the presence of subthreshold symptoms of a psychotic episode, such as unusual thought content, suspiciousness, grandiose ideas, perceptual abnormalities, or disorganised communication (Salazar de Pablo et al., 2020). APS are considered to be present if one of the symptoms listed above reaches clinically significant disturbance below psychotic intensity (McGlashan et al., 2010). Even though self-reported APS are less predictive than clinician-reported symptoms (Fusar-Poli et al., 2017), self-reported APS are still associated with a four-fold risk of subsequent hospitalisation for a psychotic disorder and a two-fold risk of hospitalisation for other mental disorders (Werbeloff et al., 2012). Accordingly, the concept of APS is a useful tool to identify individuals that have an increased risk of developing a psychotic disorder (Arango, 2011). However, as mentioned above APS are not only indicative of future psychotic disorders but are also associated with other mental disorders, making it necessary to carefully assess the diagnostic specificity of reported APS (Gaudiano & Zimmerman, 2012; Rosen et al., 2006).

Substance use and substance use disorders (SUDs) are strongly linked to psychosis and APS (Matheson et al., 2022). For instance, 50% of patients with a first episode of psychosis present with a co-occurring SUD (Brunette et al., 2018). Furthermore, the severity of SUD is positively correlated with increased APS prevalence (Smith et al., 2009).

This relationship seen in adult patients can also be observed in adolescents. Substance use, particularly cannabis and ecstasy use by adolescents, is associated with a high-risk for psychosis (Carney et al., 2017; Wiedmann, Kuitunen-Paul, et al., 2022) and admission due to psychotic symptoms (Baeza et al., 2009; Schimmelmann et al., 2012).

At present a co-occurrence of APS and SUD is commonly interpreted as an indicator of a high risk for a prodromal stage of substance-induced psychosis (Beckmann et al., 2020).

However, APS are diagnostically diverse and adolescents with SUD also present with other mental disorder (Kuitunen-Paul et al., 2021; Wiedmann, Atzendorf, et al., 2022), thus it is possible that co-occurrence of SUD and APS might be related to yet another factor.

One of these factors may be the high incidence of traumatic experiences (TEs) or post-traumatic stress disorder (PTSD) in adolescents with SUD (Basedow et al., 2020). Previous research has shown that TEs are highly prevalent in adolescent who report APS (Fusar-Poli, Tantardini, et al., 2017; Kelleher et al., 2008) and that TEs stay a significant predictor for

APS even when taking substance use into account (Wiedmann, Kuitunen-Paul, et al., 2022). Specific APS that are associated with TEs and PTSD are suspiciousness and grandiose ideas (Falukozi & Addington, 2012) as well as perceptual abnormalities (Scott et al., 2007; Simon et al., 2014). One reason why APS are related to trauma related disorders could be a trauma-induced stress sensitivity which increases the risk for later APS development through alterations of the neurobiological stress system (Holtzman et al., 2013). In previous studies PTSD and TEs have often been grouped together as a single risk factor for APS, however, it remains to be investigated whether individuals with TEs but not PTSD suffer from APS at a similar rate as patients with PTSD. Thus it is not clear how the presence of TEs and/or PTSD in adolescent patients with SUD relates to prevalence of APS. This knowledge is important especially for clinicians to make correct diagnostic decisions and choose appropriate treatment strategies.

We aimed to explore if a history of TEs or a current PTSD can predict APS in adolescents with SUDs. In addition we investigated associations between past-year use estimates for different psychoactive substances and current APS.

2. Methods

2.1. Participants

Between November 2017 and December 2022, $n = 120$ treatment-seeking adolescents at a German outpatient clinic for adolescents with SUD consented to participate in the study and filled out all relevant questionnaires. Participants were divided into three groups according to their trauma status resulting from a PTSD questionnaire: patients with SUD without history of traumatic experiences ('No TEs'), patients with SUD with a history of TEs but no current PTSD ('TEs'), and patients with SUD and self-reported PTSD ('PTSD'). Notably, adolescent patients did not qualify for acute (drug-induced) psychosis or psychotic symptoms that would have required treatment.

2.2. Procedure

Data collection was embedded into the standard diagnostic procedures at the Outpatient Clinic for Adolescent Substance Abuse, University Hospital C. G. Carus Dresden, Germany, see study protocol NCT03444974 registered at clinicaltrials.gov. Questionnaires were handed out to patients and their legal guardians at the first consultation appointment. The sample was collected via consecutive admission of treatment-seeking patients. The criteria for SUDs according to ICD-10 were assessed in an admission interview by a trained clinical psychologist. The admission interview only includes a proper interview section for SUD criteria, while criteria for other mental disorders are screened for via questionnaires. The study was conducted in accordance with the Declaration of Helsinki and all procedures were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018).

2.3. Measures

Attenuated psychotic symptoms. The German 16-Item short version (PQ-16) (Ising et al., 2012) of the Prodromal Questionnaire (PQ) (Loewy et al., 2005) is a screening questionnaire assessing the presence of APS in the past month on a two-point scale (true/false) and subjective load on a four-point Likert scale ranging from 0 ('not at all') to 3 ('very much'). The PQ-16 questionnaire provides a total score for all 16 items and three additional subscales: unusual thought content/delusional ideas (5 items), perceptual abnormalities/hallucinations (9 items) and negative symptoms (2 items). The questionnaire is validated for use in adolescents with a cut-total score of 7 indicating high-risk status for psychosis (de Jong et al., 2020)

Thought problems. The Youth Self-Report (YSR/11-18) (Arbeitsgruppe Deutsche Child Behavior Checklist, 1998) is a questionnaire on which adolescents rate their behavioural, emotional, social and physical problems for the previous six months. The questionnaire consists of 120 items with three response options (0 = 'not applicable', 1 = 'sometimes', 2 = 'frequently'). For this project, we only analysed the total score on the thought problem subscale (6 items) as a dependent variable (DV).

Substance use disorder severity. The Drug Use Disorders Identification Test (DUDIT) (Voluse et al., 2012) is a self-report instrument composed of 11 items related to problems with illegal substance use, deemed reliable for the use in adolescents (Basedow, Kuitunen-Paul, Eichler, et al., 2021). Scoring of the DUDIT is two-fold: items one to nine are scored on a five-point Likert scale, while items ten and eleven are scored on a three-point scale. DV was the total DUDIT score.

Trauma status and PTSD symptoms. The German version (Ruf et al., 2011) of the Post Traumatic Stress Disorder Reaction Index for DSM-IV (Steinberg et al., 2004) is a questionnaire assessing lifetime TEs and current PTSD symptoms in adolescents. In the questionnaire, participants select the frequency of occurrence of PTSD symptoms during the past month (rated from 0 = 'none of the time' to 4 = 'most of the time'). The items map directly onto the DSM-IV intrusion (Criterion B), avoidance (Criterion C), and hyperarousal (Criterion D) symptoms. Criterion A is fulfilled if one of the listed traumatic

situations is checked off as having happened to the participant. Criterion B is fulfilled if one of five intrusion items is rated as 2 (=some of the time) or higher. Criterion C is fulfilled if three out of nine avoidance items are rated as 2 or higher. Criterion D is fulfilled if two out of six hyperarousal items are rates 2 or higher. These criteria are based on psychometric validation studies (Elhai et al., 2013; Steinberg et al., 2013) and have been applied in clinical settings (Oswald et al., 2010). Since this questionnaire is a self-report measure and does not include clinical judgment, we considered PTSD as probable and not as established when all four criteria (criterion A, B, C, & D) are fulfilled (Steinberg et al., 2004). DVs for this questionnaire were the probable presence of a PTSD (yes/no) and whether TEs were reported (yes/no).

Substance use. The pattern of substance use was assessed via an interview (Golub et al., 2021), asking for the number of days each substance was used per month over the past year and for the average quantity of used substance per day. DV from this assessment was calculated by multiplying the average number of use days with the average daily amount per substance used, resulting in the estimated average amount of substance used per month (e.g. grams of cannabis per month). Assessed substances were tobacco (cigarettes), alcohol, cannabis, ecstasy, amphetamine, and methamphetamine.

2.4. Statistical analysis

All calculations were performed with IBM SPSS 27 (IBM, 2020). Descriptive group differences in age, gender, and substance use variables were assessed with ANOVA, chi-square test and MANOVA respectively. The three groups differed only in terms of their gender distribution (see Table 1). Therefore, we performed a two-way MANOVA with group ('no TEs', 'TEs', 'PTSD') and gender (male, female) as factors and the four PQ-16 scales as outcomes. Since not all participants filled out the YSR thought problems scale, we performed a separate two-way ANOVA with only the YSR scale as outcome. When the group effect was significant, post-hoc t-tests were performed to compare the differences on the significant scale between each group, corrected for false-positives via the Bonferroni method (Bland & Altman, 1995). To investigate the association between substance use variables and each of the four PQ-16 scales as well as the YSR thought problems scale, we performed five linear regressions with substance use variables (DUDIT score, cigarette, alcohol, cannabis, ecstasy, amphetamine, methamphetamine use) as predictors.

Significance level was set to $p < .05$. Effect sizes were classified according to Cohen (1988) into small effects ($|\eta^2| \geq .01$; $|b| \geq .10$), medium effects ($|\eta^2| \geq .06$; $|b| \geq .30$), and large effects ($|\eta^2| \geq .14$; $|b| \geq .50$).

3. Results

3.1. Participants

The three groups of participants did not differ in terms of age (F (119) = 0.44, $p = .649$), but in terms of their gender distribution ($X^2(2) = 11.39$, $p = .003$), with the No TEs group having a lower percentage of female participants, see Table 1 for details.

3.2. APS in adolescents with SUD

We observed a group ('no TEs' vs. 'TEs' vs. 'PTSD') effect on PQ-16 scores among adolescent patients with SUD ($F(226) = 4.74$, $p = .0001$, $\eta^2 = .112$), but no interaction effect between group and gender (F (226) = 1.24, $p = .286$, $\eta^2 = .032$). The three groups ('no TEs', 'TEs', 'PTSD') differed in terms of their total PQ-16 score ($F(114) = 11.99$, $p = .00002$, $\eta^2 = .174$), disturbed thought content ($F(114) = 13.92$, $p = .000004$, $\eta^2 = .196$), perceptual disturbances (F (114) = 6.60, $p = .002$, $\eta^2 = .104$), and negative symptoms ($F(114) = 5.92$, $p = .004$, $\eta^2 = .094$). Furthermore, the MANOVA also showed a group effect on the YSR thought problem scale ($F(53) = 7.67$, $p = .001$, $\eta^2 = .242$) and again no interaction effect of group and gender ($F(53) = 0.27$, $p = .768$, η^2

Table 1. Demographic details of participants.

	SUD and No TEs ($n = 33$)	SUD and TEs ($n = 47$)	SUD and PTSD ($n = 40$)	Group comparison		
				Test statistic (df)	p-value	Effect size (η^2)
Age in years; M (SD)	15.8 (1.4)	15.9 (1.3)	16.1 (1.2)	F (119) = 0.44	.649	$\eta^2 = .007$
% of female patients	24.2%	38.3%	62.5%	X^2 (2) = 11.39	.003*	$V = .22$
DUDIT score; M (SD)	16.2 (10.2)	16.5 (9.8)	19.3 (11.3)	F (117) = 1.06	.350	$\eta^2 = .018$
Substance units per month over past year; M (SD)						
Number of cigarettes	275.5 (278.8)	339.1 (284.0)	311.1 (267.2)	F (75) = 0.58	.562	$\eta^2 = .016$
Alcoholic standard drinks	58.6 (116.1)	107.1 (242.1)	125.0 (205.1)	F (75) = 0.91	.405	$\eta^2 = .024$
Grams of cannabis	47.3 (86.1)	59.0 (81.0)	37.4 (49.5)	F (75) = 0.87	.425	$\eta^2 = .023$
Number of ecstasy pills	3.64 (9.6)	0.8 (1.8)	12.4 (33.1)	F (75) = 2.32	.106	$\eta^2 = .060$
Grams of amphetamine	0.9 (3.7)	1.1 (4.9)	0.4 (1.1)	F (75) = 0.52	.595	$\eta^2 = .014$
Grams of methamphetamine	0.6 (2.7)	5.8 (24.7)	9.0 (33.0)	F (75) = 0.83	.440	$\eta^2 = .022$

Note: *DUDIT*, Drug Use Disorder Identification Test; *TE*, Traumatic Event; *PTSD*, Post-traumatic stress disorder.

Table 2. Means and multiple comparisons.

	SUD and No TEs ($n = 33$)	SUD and TEs ($n = 47$)	SUD and PTSD ($n = 40$)
Means and standard deviations			
PQ-16 – total	3.27 (3.1)	3.77 (3.3)	7.00 (4.0)
PQ-16 – thought	1.30 (1.2)	1.60 (1.3)	2.90 (1.4)
PQ-16 – perceptual	1.30 (1.9)	1.64 (2.0)	3.08 (2.6)
PQ-16 – negative	0.67 (0.5)	0.53 (0.7)	1.08 (0.7)
YSR – thought problems	55.46 (6.6)	55.55 (8.3)	65.62 (8.3)
Multiple Comparisons*			
	No TEs vs. PTSD	*TEs vs. PTSD*	
PQ-16 – total	Diff. = |3.73|, t (71) = −4.41, p = .00005	Diff. = |3.23|, t (85) = −4.15, p = .0001	
PQ-16 – thought	Diff. = |1.55|, t (71) = −4.89, p = .000007	Diff. = |1.25|, t (85) = −4.33, p = .00007	
PQ-16 – perceptual	Diff. = |1.77|, t (71) = −3.24, p = .003	Diff. = |1.44|, t (85) = −2.90, p = .010	
PQ-16 – negative	Diff. = |0.41|, t (71) = −2.67, p = .029	Diff. = |0.54|, t (85) = −3.57, p = .0006	
YSR – thought problems	Diff. = |10.16|, t (32) = −3.73, p = .003	Diff. = |10.07|, t (39) = −3.88, p = .0007	

Note: *only statistically significant post-hoc tests are displayed. All comparisons between the 'no TEs' and 'TE' group were non-significant. *PQ-16*, Prodromal Questionnaire 16-item version; *YSR*, Youth Safe Report; *TE*, Traumatic Event; *PTSD*, Post-traumatic stress disorder; *Diff.*, mean difference between groups.

= .011). Based on their effect sizes, all effects are at least of medium size, and the group differences in total PQ-16 score, disturbed thought content and YSR thought problems were large. Post-hoc analysis revealed that the 'PTSD' group scored higher on each PQ-16 subscale as well as the YSR thought problem scale, compared to the 'No TEs' and 'TEs' group, see Table 2. All comparisons between the 'no TEs' and 'TEs' group were not statistically significant.

3.3. Association of substance use with APS

Substance use variables (tobacco, alcohol, cannabis, ecstasy, amphetamine, methamphetamine use) were not significantly associated with PQ-16 total score ($F(75) = 0.42$; $p = .86$; $R^2 = .04$), PQ-16 thought disturbance ($F(75) = 0.64$; $p = .70$; $R^2 = .05$), PQ-16 perceptual symptoms ($F(75) = 0.43$; $p = .86$; $R^2 = .04$), PQ-16 negative symptoms ($F(75) = 0.22$; $p = .75$; $R^2 = .05$), or YSR thought problems ($F(35) = 2.31$; $p = .06$; $R^2 = .32$). See Table 3, for an overview over standardised coefficients and test results for each variable in each regression model.

4. Discussion

In the present study, we investigated whether the extent of APS is associated with a lifetime history of TEs or an additional self-reported PTSD in adolescent SUD outpatients without acute psychotic symptoms. We showed that patients with the combination of SUD and self-reported PTSD show higher levels of APS in each assessed domain than patients with SUD without self-reported PTSD even if they have a lifetime history of TEs. The frequency of substance use and severity of SUD were not related to levels of APS.

On one hand these results confirm previous findings relating the presence of PTSD to an increased level of APS (Simon et al., 2014) and indicate that an increased level of APS in adolescent patients with SUD might be due to this association. Patients with a history of TEs but not PTSD might also be exposed to protective factors, such as social support (McCrory et al., 2022), that protect from development of PTSD as well as APS.

Furthermore, our findings are not in line with findings associating substance use, and ecstasy use specifically, with APS. For example, case reports indicate that ecstasy users might develop psychotic-like symptoms or depersonalisation (Majić et al., 2022; Vaiva et al., 2001; Virani et al., 2018) and empirical studies have shown an association between ecstasy use and APS (Duman et al., 2017; Wiedmann, Kuitunen-Paul, et al., 2022), as well as ecstasy use and PTSD (Basedow et al., 2022; Basedow, Kuitunen-Paul, Wiedmann, et al., 2021). One reason for this discrepancy might be the specific form of assessment and inclusion criteria applied in our study. First, our main outcome variable (PQ-16 score) only assesses APS occurrence in the past month. Second, patients with acute psychotic state were not admitted to our clinic, excluding them from participation in this study. Therefore, it is possible that substance-induced APS are indeed rare and instead substance use is more strongly related to fully developed psychotic symptoms.

Table 3. Regression coefficients for the five performed regression analyses.

	PQ-16 – total	PQ-16 – thought	PQ-16 – perceptual	PQ-16 – negative	YSR – thought problems
Tobacco	$b = -.075$; $p = .628$	$b = -.067$; $p = .666$	$b = -.031$; $p = .840$	$b = -.091$; $p = .555$	$b = -.347$; $p = .109$
Alcohol	$b = .104$; $p = .474$	$b = .034$; $p = .813$	$b = -.067$; $p = .648$	$b = .164$; $p = .262$	$b = .342$; $p = .094$
Cannabis	$b = .154$; $p = .205$	$b = .138$; $p = .260$	$b = .105$; $p = .392$	$b = .059$; $p = .626$	$b = .177$; $p = .280$
Ecstasy	$b = -007$; $p = .952$	$b = -.025$; $p = .842$	$b = -.058$; $p = .643$	$b = .034$; $p = .783$	$b = .451$; $p = .007$
Amphetamine	$b = -.128$; $p = .287$	$b = -.111$; $p = .360$	$b = -.085$; $p = .483$	$b = -.036$; $p = .766$	$b = -.263$; $p = .140$
Methamphetamine	$b = .123$; $p = .319$	$b = .100$; $p = .423$	$b = .118$; $p = .346$	$b = -.118$; $p = .342$	$b = .034$; $p = .851$

Note: *PQ-16*, Prodromal Questionnaire 16-item version; *YSR*, Youth Safe Report.

However, when investigating the substance-specific relationship between use frequency and APS, we found no association between ecstasy use (or other substances for that matter) and APS scores in our data. This is a further indication, that APS might be specifically related to the presence of PTSD, while fully developed psychotic syndromes might be more reliably induced by substance use.

This conclusion is also in line with previous research that has shown that TEs in childhood and subsequent PTSD increase the risk of experiencing APS (Frydecka et al., 2020; Hodgekins et al., 2018; Varese et al., 2012) and are a stronger predictor of APS than substance use (Mongan et al., 2019). The association of PTSD with APS in patients with SUD might be mediated by symptoms of borderline personality disorder, disturbances of self (e.g. depersonalisation or derealization) and cognitive biases, all of which have been associated with APS (Gawęda et al., 2019; Pionke-Ubych et al., 2021; Sengutta et al., 2019). Specifically, disturbed social processes and attachment issues as seen in borderline personality disorders are also prevalent in SUDs (Gąsior, 2018; Hanegraaf et al., 2021) while cognitive biases play a major role in the development of SUDs (McCusker, 2001) and are an important target for novel SUD interventions (Cristea et al., 2016; Wiers et al., 2013). These connections support the notion that PTSD induces alterations in social and cognitive processes that in turn increase the likelihood of subsequent APS and SUD development, therefore indicating that APS in adolescent patients with SUD might reflect a presence of PTSD rather than a prodromal substance-induced psychosis. This line of reasoning is supported by other research indicating that APS are not necessarily an indication of clinically verified psychotic experience but can be seen as more general markers of psychopathology (Moriyama et al., 2019).

4.1. Limitations

First, this study is an analysis of cross-sectional data prohibiting us from drawing any causal inference. Accordingly, we describe two opposing potential explanations for our findings and propose that future studies assess PTSD symptoms, APS, and substance use continuously and longitudinally to investigate causal pathways. Especially important are assessments that allow conclusions about times of symptom (PTSD, SUD and APS) onset and the timing of TEs.

Second, the groups differ in terms of their gender distribution. While we aimed to correct for this imbalance using appropriate statistical methods, this might indicate that the groups differ in additional sociodemographic aspects we have not assessed.

Third, APS might lead to and overlap with substance-induced psychotic symptoms and psychoses. Especially in genetically vulnerable adolescents, the use of psychoactive substances such as cannabis, ecstasy, or methamphetamine could contribute to such symptoms and diagnoses (Beckmann et al., 2020). However, none of our SUD outpatients presented acute psychotic symptoms. Even if, these patients would have been transferred to acute inpatient treatment. Lacking these patients thus increases the chance to miss an otherwise present association between SUD, PTSD and APS.

4.2. Clinical implications

Our results indicate that, in adolescent patients that report APS and co-occurring substance use, an assessment of TEs and PTSD is always indicated for a proper differential diagnosis. An integrated treatment of PTSD and SUD is not only warranted given the high comorbidity (Kuitunen-Paul et al., 2021; Wiedmann, Atzendorf, et al., 2022), it may also be possible, albeit this hast to be tested, that that APS might be indirectly alleviated by an integrated treatment of SUD and PTSD. A psychotherapeutic approach integrating therapy for symptoms from different disorders is even more important, given that pharmacological treatment options for either of these disorders and symptoms are heavily limited (Cohen et al., 2010).

5. Conclusion

APS in adolescents with SUD seem to be more strongly related to PTSD symptom than substance use. PTSD and a strong prevalence of TEs might be a better explanation for the occurrence of APS in adolescents with SUD than the frequency or type of substance use. Clinicians should take care to exclude the possibility of APS being related to a presence of PTSD when suspecting a case of substance-induced psychosis.

Ethics approval and consent to participate

All procedures of this study were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018). Patients as well as legal guardians were informed about the projects thoroughly and comprehensively. Written informed consent was obtained from all legal guardians.

Author Contribution

LAB analysed the data and wrote the manuscript. MFW participated in writing the manuscript, data analysis, and contributed to the discussion. VR and SKP participated in writing the manuscript and contributed to discussion. YG designed the study,

participated in writing the manuscript and contributed to discussion.

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No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and analysed during the current study are available from the corresponding author (LAB) on reasonable request.

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