Journal of Psychiatric Research 189 (2025) 325–334

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Alexithymia and psychopathological dimensions in First-Episode Psychosis: Comparative patterns in natural cannabis versus synthetic cannabinoid users

Ricci Valerio [a,*], Di Muzio Ilenia [b], Mancusi Gianluca [b,c], Ceci Franca [b], Ciavarella Maria Celeste [c], Di Carlo Francesco [c], Pettorruso Mauro [c], Martinotti Giovanni [c], Maina Giuseppe [a]

[a] Department of Neuroscience, San Luigi Gonzaga University Hospital, 10043, Orbassano, Italy
[b] Department of Mental Health, ASL Lanciano-Vasto-Chieti, Chieti, Italy
[c] Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio Chieti-Pescara, 66100, Chieti, Italy

ARTICLE INFO

Keywords:
Cannabis use disorder (CUD)
Synthetic cannabinoids (SCs)
Natural cannabis (NC)
Alexithymia
Aberrant salience
First episode psychosis (FEP)

ABSTRACT

Aims: This study aimed to investigate the differences in psychotic symptomatology, dissociative symptoms, alexithymia, and aberrant salience among three groups: non-cannabis users (NU), natural cannabis users (NC), and synthetic cannabinoid users (SCs). The study also explored the patterns of alexithymia and its associations with other psychopathological dimensions in these populations.

Methods: A total of 108 participants experiencing First Episode Psychosis (FEP) were recruited during psychiatric crisis presentations to emergency rooms in Italy and categorized into three groups (NU, NC, SCs; n = 36 each). Participants were initially assessed 48–72 h after inpatient admission following clinical stabilization. Psychopathological assessments were conducted using the Positive and Negative Syndrome Scale (PANSS), Dissociative Experiences Scale (DES-II), Aberrant Salience Inventory (ASI), and Toronto Alexithymia Scale (TAS-20). Evaluations occurred at baseline (T0), three months (T1), and six months (T2) post-admission. Statistical analyses included ANOVA and repeated-measures ANOVA comparisons across time points.

Results: SC users exhibited significantly higher positive psychotic symptoms, persistent aberrant salience, and limited recovery of alexithymia compared to NC users and non-users. Dissociative symptoms were more prominent in both NC and SCs users, with SCs users showing minimal improvement over time. Negative symptoms were higher in non-users but showed progressive reduction across all groups. Significant correlations were observed between alexithymia and specific aberrant salience subscales, particularly Feelings of Increased Significance and Sense Sharpening.

Conclusions: Synthetic cannabinoids are associated with more severe and persistent psychotic symptoms and emotional dysregulation compared to natural cannabis. Alexithymia and dissociation showed distinct patterns across user groups, with different trajectories of change over the six-month observation period. These findings underscore the need for targeted interventions addressing emotional regulation and salience processing in cannabis-related psychosis.

1. Introduction

Cannabis, a widely used recreational drug, was consumed by 3.9 % of the global population aged 15–64 in 2018 (Ransing et al., 2021). In Italy, 32.7 % of individuals reported using cannabis at least once in their lifetime, with 43.7 % of US 12th graders reporting usage in 2020 (Hinckley et al., 2023). Its popularity arises from affordability, accessibility, and psychoactive effects such as euphoria and relaxation. However, approximately 10 % of users develop Cannabis Use Disorder (CUD), as defined by DSM-5 (American Psychiatric Association, 2013). The psychoactive effects are primarily attributed to Δ9-tetrahydrocannabinol (THC), a partial agonist of CB1 and CB2 receptors.

* Corresponding author. Psychiatry Department, San Luigi Gonzaga Hospital, Turin University; Regione Gonzole, 10, Orbassano, 10043, Turin, Italy.
E-mail address: valerio.ricci@unito.it (R. Valerio).

https://doi.org/10.1016/j.jpsychires.2025.06.025
Received 4 February 2025; Received in revised form 4 June 2025; Accepted 16 June 2025
Available online 19 June 2025

Synthetic cannabinoids (SCs), often referred to as "Spices," represent a potent class of New Psychoactive Substances (NPS) and act as full agonists of CB1 receptors. Unlike natural cannabis (NC), SCs are associated with severe symptoms such as anxiety, paranoia, and tachycardia (Scherbaum et al., 2017; EMCDDA, 2023; Elsohly ET AL, 2014; Hindson et al., 2023). SCs are increasingly prevalent due to their availability as "legal highs" and their potent psychoactive effects, posing significant health risks (EMCDDA, 2023). Both NC and SCs disrupt dopamine, GABA, and glutamate systems, contributing to psychosis through mechanisms involving mesolimbic dopaminergic activity and NMDA receptor disruption (D'Souza DC et al., 2009; Martinotti et al., 2021a; Sherif et al., 2018).

Psychosis is characterized by disturbances in reality perception, including hallucinations, delusions, and disorganized thinking. Cannabis use has been strongly linked to the development of psychosis, particularly First Episode Psychosis (FEP), with SCs carrying a higher risk compared to NC (Reed, 2008; Schimmelmann et al., 2011; Papanti et al., 2013). Cannabis-related psychosis shows persistent symptoms, longer hospitalizations, and poorer outcomes (Ricci et al., 2023; Quattrone et al., 2021; Schoeler et al., 2017). Recent studies highlight dissociative symptoms, such as derealization and depersonalization, as significant components of cannabis-related psychosis. Dissociative symptoms are often more persistent in NC users compared to non-users, emphasizing the nuanced psychopathological profiles across substance types (Altintas et al., 2016; Seddon et al., 2016).

The concept of Aberrant Salience (AS) provides a cognitive framework for understanding the development of psychosis. AS involves attributing undue significance to irrelevant stimuli, a process driven by dopaminergic dysregulation. Elevated AS is frequently observed in cannabis users and is linked to positive psychotic symptoms (Poletti et al., 2022; Pugliese et al., 2022; Patti et al., 2022). Cicero et al. (2010) introduced the Aberrant Salience Inventory (ASI) scale, a self-reported questionnaire. The ASI is scored based on five correlated subscales: Feelings of Increased Significance (FIS) heightened salience to otherwise innocuous stimuli; Sense Sharpening (SS), anomalies of perception; Impending Understanding (IU), (heightened salience leading to a breakthrough in understanding); Heightened Emotionality (HE) and Heightened Cognition (HC) (the efforts to comprehend emotions and thoughts accompanying AS experiences, which may also relate to pre-psychotic experiences). Elevated scores on ASI scale have been linked with psychosis proneness, which includes schizotypy or schizotypal traits (Cicero et al., 2010). Furthermore a positive correlation was found between AS and the number of years of cannabis use and the frequency of use (Anglin et al., 2021). A recent study showed higher levels of AS in SPICE-users and a minor reduction after pharmacological treatment compared to the other two study groups, cannabis users and non-users (Ricci et al., 2024).

Alexithymia, introduced by Sifneos in the 1970s, describes difficulties in identifying and expressing emotions, distinguishing them from physiological sensations, and a preference for externally oriented thinking (Sifneos, 1973). While typically considered a stable trait, alexithymia can be exacerbated by substance use (Robinson and Berridge, 1993; Mattila et al., 2007)]. Studies suggest high alexithymia prevalence among patients with Substance Use Disorders (SUDs), including CUD, where it correlates with emotional dysregulation, impulsivity, and aggression (Fossati et al., 2009; Parolin et al., 2018; Cruise and Becerra, 2018). Alexithymia in schizophrenia and psychosis is linked to negative symptoms, poorer social functioning, and increased suicidality, although conflicting findings exist regarding its association with symptom severity (Taylor et al., 1997; Salminen et al., 1999; Lane et al., 1998; Stanghellini and Ricca, 1995).

Beyond their pharmacological differences, users of NC and SCs may also differ in terms of personality traits and psychological characteristics. Research suggests that individuals who seek more potent substances like SCs often display higher sensation-seeking behavior, greater impulsivity, and increased risk-taking tendencies (Baler and Volkow, 2011; Zuckerman and Kuhlman, 2000). Furthermore, people with pre-existing difficulties in emotional regulation and alexithymic traits may preferentially choose more potent substances for their stronger and immediate psychoactive effects, potentially as a maladaptive coping strategy for emotional distress (Thorberg et al., 2009). These distinct psychological profiles could interact with the neurobiological effects of cannabinoids to produce different patterns of psychopathology and recovery trajectories. Understanding these personality-substance interactions provides a theoretical framework for expecting differences between NC and SCs users in both acute presentation and long-term outcomes.

The study aims to differentiate psychoses not associated with cannabis use and those linked to the consumption of NC and SCs in terms of: (a) Positive and Negative Syndrome Scale (PANSS) for investigating psychotic symptoms, (b) the Dissociative Experiences Scale (DES-II) for measuring dissociative symptoms, (c) ASI scale for gauging AS, and (d) the Toronto Alexithymia Scale (TAS-20) for measuring Alexithymia. Additionally, we aimed to investigate more thoroughly the role of Alexithymia in the origin and progression of non-cannabis-induced psychosis and whether Alexithymia also plays a role in the onset and course of NC and SCs-induced psychosis. Given the lack of robust literature supporting this concept, we set out to examine the relationships between Alexithymia and PANSS and between Alexithymia and DES II.

2. Material and methods

2.1. Participants

The study included one hundred eight subjects who had experienced FEP and were recruited during the acute phase of their psychosis from hospital emergency rooms in the Italian regions of Val d'Aosta and Piemonte, spanning from 2015 to 2024. Patients presenting with acute psychotic symptoms were initially evaluated by psychiatric emergency staff. After initial clinical stabilization (typically within 24–48 h after admission), eligible patients were approached by a member of the research team who provided information about the study. For those who expressed interest and demonstrated capacity to provide consent, the informed consent process was completed, followed by screening assessments to confirm eligibility.

Approximately 210 patients with acute psychotic symptoms were initially identified by emergency department staff as potentially eligible based on preliminary clinical assessment. Of these, 57 were excluded before formal approach by our research team based on medical records review and information from treating clinicians that indicated they clearly met exclusion criteria (previous formal treatment for psychosis, intellectual disability, significant medical illness, or regular use of substances other than cannabis). During the recruitment period, we approached 153 potential participants who met initial screening criteria. Of these, 27 declined participation, 18 were unable to provide valid informed consent due to the severity of psychotic symptoms or cognitive impairment, and 108 were successfully enrolled in the study, representing a 70.6 % participation rate among eligible patients. Eligibility screening and T0 assessments were conducted after patients' clinical stabilization, typically 48–72 h post-emergency room admission and after initiating antipsychotic treatment. Assessments were performed in the psychiatric inpatient unit by trained psychiatrists. This timing ensured participants could provide reliable responses while still capturing data representative of their acute presentation.

Inclusion criteria: Age between 16 and 50 years, Diagnosis of schizophrenia spectrum disorder or another non-affective psychotic disorder based on DSM-5 criteria (4), Individuals with a diagnosis of CUD needed a history of frequent cannabis use (2–3 times per week), Individuals without a diagnosis of NC/SCs use disorder were required to have no lifetime use of NC or SCs, Primary residence within the recruiting area.

Exclusion criteria: individuals who had previously received formal

treatment for psychosis from mental health services and who had received prior continuous treatment with antipsychotic medications for more than two weeks, individuals with intellectual disability (QI score less than 70), Any lifetime history of significant medical illness. Participants reporting the use of substances other than cannabis at a frequency greater than once a month, Individuals with an alcohol use disorder.

While all participants met broad DSM-5 criteria for schizophrenia spectrum and other non-affective psychotic disorders, specific disorder subtypes were not systematically differentiated for this study. This methodological choice ensured diagnostic consistency across groups and avoided potential bias from substance-related factors during acute presentation. All participants were therefore analyzed as FEP cases. For the purpose of this study, FEP was operationalized as the first presentation to psychiatric services requiring formal intervention for psychotic symptoms, regardless of the duration of untreated psychosis. Participants were assessed and treated according to the standard protocol for FEP management at our participating centers. This approach reflects local clinical practices where patients experiencing acute psychosis were initially evaluated in emergency departments, stabilized in psychiatric inpatient units, and followed up through our integrated clinical-research network, which facilitated assessments at T1 and T2.

Participants were assigned to three groups based on their self-reported substance use history: non-users (NU), who had no lifetime history of cannabis use; natural cannabis users (NC), who reported regular use of cannabis; and synthetic cannabinoid users (SCs), who reported regular use of synthetic cannabinoids. Group assignment was based solely on substance use patterns, confirmed through clinical interviews and standardized assessments (DAST-10 and CUDIT-R). The recruitment continued until we reached sufficient numbers in each group, resulting in three groups of 36 participants each. Post-hoc analysis revealed that the groups had comparable age and sex distributions, though this was not achieved through formal stratification. This natural balance in demographics helped minimize potential confounding effects of age and sex on our outcome measures.

2.2. Measurements

Participants were subjected to different psychopathological scales at three different times (T0, T1 and T2).

- The PANSS (Kay et al., 1987), a 30-item questionnaire, divided into three subscales, measuring positive and negative symptoms and the general severity of illness.
- The Dissociative Experience Scale (DES II) (Bernstein and Putnam, 1986), a self-report questionnaire measuring dissociative experiences, such as derealization, n, absorption, and amnesia The DES comprises 28 items based on the assumption of a 'dissociative continuum' ranging from a mild alteration to severe dissociation. ,
- Aberrant Salience Inventory (ASI) (Cicero et al., 2010), a self-reported questionnaire, based on five correlated subscales: FIS, SS, IU, HE, HC. These relate AS respectively with otherwise innocuous stimuli, anomalies of perception, a breakthrough in understanding, emotions and thoughts (25).
- Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994), a self-report questionnaire is comprised of 20 items rated on 5-point Likert scales ranging from 1 (strongly disagree) to 5 (strongly agree). The TAS-20 consists of 3 factors: difficulty identifying feelings (DIF); difficulty describing feelings (DDF); externally oriented cognitive style of thinking (EOT).

Information about previous mental health services, diagnoses, and medication history was collected through a structured clinical interview conducted by trained psychiatrists. Medical records from referring emergency departments were reviewed when available. This information was cross-validated through collateral sources (family members or caregivers) when possible, particularly regarding medication adherence and substance use patterns. Family members provided additional context about patients' substance use history, particularly in cases where self-reporting was unclear or when patients expressed uncertainty due to their acute state. This information complemented self-reports, standardized assessments, and when available, toxicology screening results. We collected information from multiple sources including friends and partners when possible, emphasizing confidentiality throughout to encourage accurate disclosure. Clinical judgment was applied to integrate different information sources.

In the study, all patients received antipsychotic treatments tailored to their medical history and condition, following clinical guidelines. Prospective evaluations occurred at two time points: after 3 months (T1) and after 6 months (T2). These assessments aimed to gauge the initial effects of treatment and the discontinuation of NC and SCs at T1, as well as the individuals' conditions after a period of relative stabilization at T2. This timeline allowed researchers to monitor changes and progress over time in response to treatment and abstinence from cannabis use. Substance use was evaluated through a comprehensive assessment of participants' substance use history, including the Drug Abuse Screening Test-10 (DAST-10), a general tool for assessing drug-related issues (Skinner et al., 1982). The use of NC and SCs was assessed using the Cannabis Use Disorders Identification Test-Revised (CUDIT-R), designed to screen for CUD (Saunders and Sellman, 2003).

2.3. Ethics statement

The study was explained in depth and all participants gave written informed consent. The study was approved by the SS. Annunziata Hospital – University G. D'Annunzio Ethical Committee (reference code: CHPN189, January 26, 2012).

2.4. Statistical analysis

The Shapiro–Wilk test was employed to assess the normality of data distribution for continuous variables. For normally distributed continuous variables, comparisons among groups (NU, NC, SC) were conducted using one-way Analysis of Variance (ANOVA) followed by Tukey's post-hoc test for pairwise comparisons. Categorical variables, including sex and marital status, were analyzed using the Chi-square test or Fisher's exact test when appropriate. Group comparisons for age were performed using ANOVA, with results expressed as mean ± standard deviation (SD). Sex and marital status distributions across groups were compared using the Chi-square test. Given the significant baseline age differences between groups ($F = 4.999$, $p = 0.008$), age was included as a covariate in all analyses. Longitudinal data across three time points (T0, T1, T2) were analyzed using repeated-measures ANCOVA with age as covariate to evaluate within-group and between-group differences over time while controlling for baseline age differences. Post-hoc analyses were conducted using Tukey's HSD test for multiple comparisons when significant main effects or interactions were found. Effect sizes were reported using partial eta-squared (η^2p). The significance level was set at $p < 0.05$ for all analyses. The relationships between continuous variables were assessed using Spearman's rho correlation. Quantitative data were presented as mean ± SD, while categorical data were reported as frequencies and percentages. The significance level was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.

The study achieved a high rate of data completeness across all time points. At T0, we had complete data for all 108 participants across all assessments. At T1, 106 participants (98.1 %) completed all assessments, with 2 participants from the SC group missing the DES-II assessment due to scheduling conflicts. At T2, 105 participants (97.2 %) completed all assessments, with 3 participants (1 from NC group and 2 from SC group) missing one or more assessments due to relocation or withdrawal from the study. The overall attrition rate was 2.8 %, with no significant differences in dropout rates between groups (Fisher's exact

test, p = 0.76). Missing data was handled using pairwise deletion in the statistical analyses. Sensitivity analyses comparing results with and without imputation of missing values showed no significant differences in outcomes, supporting the robustness of our findings.

3. Results

3.1. Demographics and cannabis use

For this study, 108 subjects (N = 108, of whom 53 were male) with acute psychosis were analyzed, classified into three groups of 36: Non-User (NU), Natural Cannabis (NC), and Synthetic Cannabinoids (SC). The groups were comparable for sex (Chi-squared test, $X^2 = 1.408$, p = 0.495) but differed significantly in age (ANOVA, F = 4.999, p = 0.008), with SC users being younger than both NU and NC users (post-hoc: NU > SC, NC > SC). Therefore, age was included as a covariate in all subsequent analyses. Demographics are in Table 1. Subjects underwent interviews, medical history collection, and clinical assessments. NC users started at 19.56 ± 5.56 years, SC users at 17.97 ± 2.71 years. First lifetime psychotic symptoms occurred in 66 subjects (61.1 %), while 42 subjects (38.9 %) had experienced previous untreated psychotic symptoms without formal psychiatric intervention prior to this presentation. All participants met our operational definition of FEP as this was their first contact with psychiatric services leading to formal treatment for psychosis. Antipsychotic treatments included haloperidol (n = 17), (n = 13,Olanzapine 9 and Quetiapine 4), -dones (n = 29, 21 with risperidone and 8 with paliperidone), and D2-partial agonists (n = 16, 14 with Aripiprazole and 2 with Brexpiprazole). Positive family history (schizophrenia spectrum disorders, schizoaffective disorder, or other non-affective psychoses) was present in 52.7 %. Clinical and psychometric data (TAS-20, PANSS, DES-2, ASI) were assessed at admission (T0), three months (T1), and six months (T2).

Table 1
Demographic and clinical characteristics of the sample.

	Non Users (n = 36)	Natural Cannabis users (n = 36)	Synthetic Cannabinoids users (n = 36)	p	Post-hoc
Age (years)	26.33 ± 5.84	25.63 ± 6.61	22.33 ± 4.55	0.008	NU > SC; NC > SC
Sex (M)	18 (50.0 %)	15 (41.7 %)	20 (55.6 %)	0.495	
Marital status (single)	26 (72.2 %)	28 (77.8 %)	31 (86.1 %)	0.350	
Previously diagnosed psychosis (yes)	14 (38.9 %)	11 (30.6 %)	17 (47.2 %)	0.349	
Antipsychotic drugs administered				0.738	
> Haloperidol	4 (11.1 %)	5 (13.9 %)	8 (22.2 %)		
> Atypical antipsychotics (-pines)	4 (11.1 %)	6 (16.7 %)	3 (8.3 %)		
> Benzisoxazole derivatives (-dones)	12 (33.3 %)	8 (22.2 %)	9 (25.0 %)		
> Partial agonists	16 (44.4 %)	17 (47.2 %)	16 (44.4 %)		
Family history for psychosis (yes)	21 (58.3 %)	18 (50.0 %)	18 (50.0 %)	0.716	

Statistics: Chi-Square Test, One-way ANOVA with Tukey post-hoc test.
Notes: pines: quetiapine, olanzapine; -dones: risperidone, paliperidone; partial agonists: aripiprazole, brexpiprazole. All participants met criteria for First Episode Psychosis; specific psychotic disorder subtypes were not systematically assessed during acute presentation to maintain diagnostic consistency and avoid potential bias from substance-related factors.

3.2. Toronto Alexithymia scale (TAS-20)

The mean values, standard deviation, and standard error of the TAS-20 scale are reported in Table 2; the temporal trend of the values is shown in Fig. 1. Post-hoc comparisons between the different groups at the various time points are presented in Table 2. The initial mean score of alexithymia was high for all three groups at T0, with slightly varying levels that did not reach statistical significance. In the post-hoc comparison, the alexithymia scores of the NU group showed a significant reduction at T1 (t = 6.787, p < 0.001) and further decreased at T2 (t = 9.378, p < 0.001), reaching a significantly lower value compared to both user groups by the end of the observation period. For both the NC and SC groups, the initial and final mean scores did not differ significantly, indicating the persistence of comparable levels of alexithymia throughout the observation period. Additionally, as confirmed in the post-hoc analysis, no significant differences were observed in alexithymic manifestations at T0 between any of the groups.

3.3. Positive and Negative Syndrome Scale (PANSS)

Table 2 presents the mean values, standard deviation, and standard error of the PANSS scale for both positive and negative subscales, including post-hoc comparisons between groups across all time points. Considering the PANSS scale for positive symptoms, persistently high levels were observed in the SC group throughout the observation period, whereas a clear and significant reduction was noted at T1 and T2 in the NU group (T1: t = 6.893, p < 0.001; T2: t = 16.629, p < 0.001) and in the NC group (T1: t = 6.254, p < 0.001; T2: t = 13.218, p < 0.001). For the PANSS scale assessing negative symptoms, a progressive and significant reduction was observed across all three groups throughout the observation period (Table 2). Moreover, analysis of the PANSS negative subscale revealed that the NU group consistently exhibited higher scores across all three assessments (T0, T1, T2) compared to the other two groups, with statistically significant differences observed in post-hoc analysis between the NU and SCs groups (p < 0.001). Therefore, negative psychotic symptoms associated with SCs were less severe than non-cannabis-induced psychosis.

3.4. Dissociative Experiences Scale (DES-II)

The mean values, standard deviation, and standard error of the DES-II scale are reported in Table 2, with the temporal trend shown in Fig. 2 and post-hoc comparisons between groups at various time points. Analysis of dissociation scale values revealed significantly higher mean scores in user groups (NC and SC) compared to the NU group. Both user groups showed a similar DES-II trend throughout observations, highlighting the pronounced dissociative effects of cannabis. During the observation period, the NU group showed a substantial reduction in mean dissociation scores at T1 (t = 7.52, p < 0.001) and T2 (t = 13.568, p < 0.001). The NC group showed a non-significant reduction at T1 (t = 2.125, p = 0.459), followed by a significant decrease at T2 (t = 4.959, p < 0.001). The SC group showed a minimal but significant reduction between T0 and T2 (t = 7.247, p < 0.001). These findings confirm an overall reduction in mean DES-II scores, with a greater decline in the NU group.

3.5. ASI and correlations with TAS-20

The mean values, standard deviation, and standard error of the ASI

Table 2
Longitudinal psychometric assessment with repeated-measures ANCOVA results (age as covariate).

Scale	Time	Non users (n = 36)	Natural Cannabis users (n = 36)	Synthetic Cannabinoids users (n = 36)
TAS-20	T0	53.61 ± 11.90	55.47 ± 8.64	57.14 ± 6.99
	T1	49.02 ± 9.97	54.94 ± 7.60	56.58 ± 6.35
	T2	47.28 ± 10.43	56.64 ± 7.62	56.17 ± 6.66
PANSS-positive	T0	23.00 ± 4.23	24.06 ± 4.11	27.03 ± 3.65
	T1	20.31 ± 4.40	21.61 ± 4.18	26.06 ± 3.82
	T2	16.50 ± 4.16	18.89 ± 3.96	25.94 ± 4.00
PANSS-negative	T0	19.39 ± 3.36	17.86 ± 3.00	14.22 ± 2.86
	T1	17.69 ± 3.42	16.61 ± 2.79	13.11 ± 2.74
	T2	15.75 ± 4.37	15.22 ± 2.83	11.92 ± 3.00
DES-II	T0	25.56 ± 5.95	35.25 ± 9.90	35.19 ± 9.32
	T1	21.72 ± 5.80	34.17 ± 9.82	32.89 ± 8.75
	T2	18.64 ± 5.64	32.72 ± 9.79	31.50 ± 8.46
ASI	T0	15.92 ± 3.55	17.44 ± 3.65	20.14 ± 3.95
	T1	13.97 ± 3.73	15.89 ± 3.49	19.08 ± 3.67
	T2	11.06 ± 3.50	14.83 ± 3.98	18.61 ± 3.76

ANCOVA Results:

Scale	Time Effect	Time × Group Interaction	Group Effect
	F (p-value) η^2p	F (p-value) η^2p	F (p-value) η^2p
TAS-20	5.89 (0.006) 0.054	18.22 (<0.001) 0.259	6.44 (0.002) 0.110
PANSS-positive	6.53 (0.006) 0.059	23.53 (<0.001) 0.312	22.36 (<0.001) 0.298
PANSS-negative	0.30 (0.679) 0.003	1.39 (0.249) 0.026	17.94 (<0.001) 0.257
DES-II	1.47 (0.233) 0.014	9.59 (<0.001) 0.156	23.12 (<0.001) 0.308
ASI	4.00 (0.026) 0.037	13.82 (<0.001) 0.210	19.98 (<0.001) 0.278

Statistics: Repeated-measures ANCOVA with age as covariate.
Notes: TAS-20: Toronto Alexithymia Scale; PANSS: Positive and Negative Syndrome Scale; DES-II: Dissociative Experiences Scale; ASI: Aberrant Salience Inventory. T0: baseline; T1: 3 months; T2: 6 months.

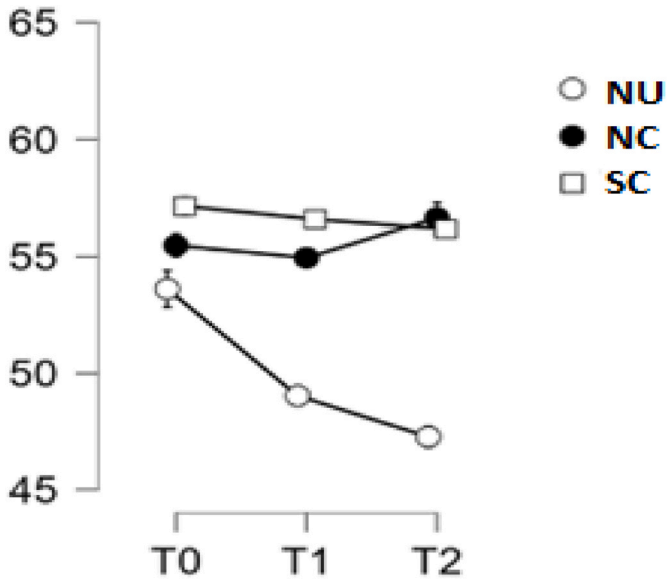

Fig. 1. TAS-20 scores. This figure illustrates the variations in mean scores of the TAS-20 scale across the three observation points T0 (baseline), T1 (3 months) and T2 (6 months) for the three groups Non Users (NU), Natural Cannabis users (NC) and Synthetic Cannabinoid users (SC). A significant reduction in TAS-20 scale values over time is observed in the NC group compared to NC and SC groups.

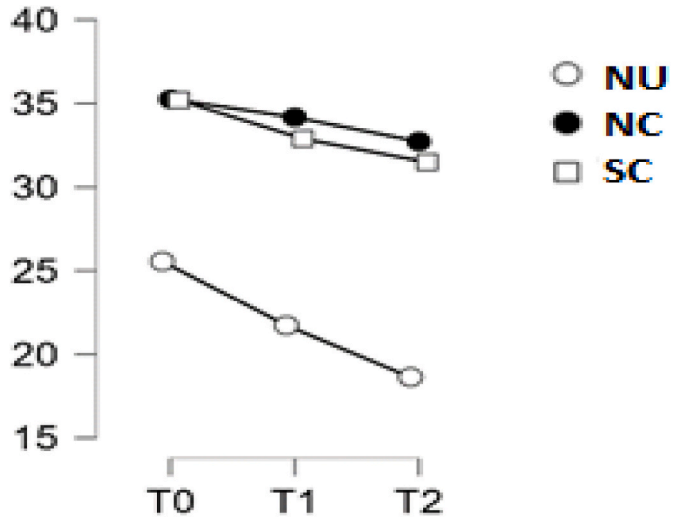

Fig. 2. DES-II scores. This image illustrates the variations in mean scores of the DES-II scale across the three observation point T0 (baseline), T1 (3 months), and T2 (6 months) for the three groups Non Users (NU), Natural Cannabis users (NC) and Synthetic Cannabinoid users (SC). The NU group exhibited significantly lower dissociation scores compared to NC and SC groups at T0, with a further reduction observed over the subsequent time points.

scale and post-hoc comparisons between groups at various time points are reported in Table 2. Spearman's correlations between TAS-20 and ASI scales/subscales are presented in Table 3. Aberrant salience, assessed using the ASI scale, showed a decreasing trend over the observation period across all groups, with a more pronounced reduction in the NU group. This trend was evident in the overall ASI score and subscales (Fig. 3). These findings highlight that aberrant salience features are more prominent during psychotic episodes and improve with symptom remission. While no significant differences in ASI values were observed between the NU and NC groups, significant differences were found between the NU and SC groups (T0: $t = -4.84$, $p < 0.001$; T1: $t = 5.859$, $p < 0.001$; T2: $t = -8.661$, $p < 0.001$), indicating a significant impact of synthetic cannabinoids on increasing aberrant salience. To investigate the relationship between alexithymia and aberrant salience, a Spearman correlation test at T0 found no significant correlations between general ASI scores and TAS-II values but significant correlations with subscales FIS (rho = 0.196, p = 0.04) and SS (rho = 0.198, p = 0.04) (Table 3).

Table 3
Spearman's correlation between TAS-20 and ASI scale and subscales.

		ASI Total	FIS	SS	IU	HE	HC
TAS-20	Spearman's rho	0.122	0.196	0.198	0.175	0.010	−0.036
	p-value	0.208	0.042*	0.040*	0.070	0.919	0.715

Notes: *p < 0.05. ASI: Aberrant Salience Inventory; FIS: Feelings of Increased Significance; SS: Sense Sharpening; IU: Impending Understanding; HE: Heightened Emotionality; HC: Heightened Cognition; TAS-20: Toronto Alexithymia Scale.

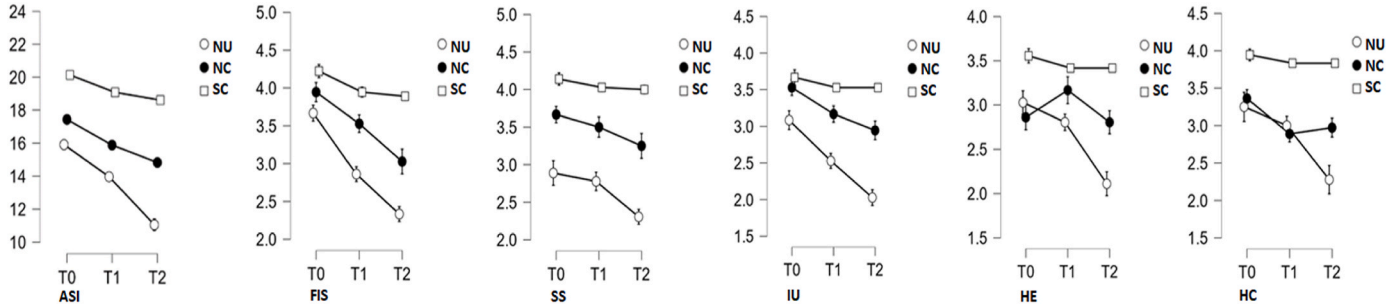

Fig. 3. The figure illustrates the temporal trends in Aberrant Salience Inventory (ASI) total scores and its subscales, including Feeling of Increased Significance (FIS), Sense Sharpening (SS), Impending Understanding (IU), Heightened Emotionality (HE), and Heightened Cognition (HC), at baseline (T0), three months (T1), and six months (T2) for non-users (circle, NU), natural cannabis users (filled circle, NC), and synthetic cannabinoid users (square, SC).

3.6. Summary of longitudinal patterns

Analyzing temporal patterns across all measures revealed distinct trajectories for the three groups. Non-users showed significant improvement across all psychopathological dimensions, with substantial reductions in positive symptoms (PANSS), dissociative symptoms (DES-II), aberrant salience (ASI), and alexithymia (TAS-20) by T2. Natural cannabis users demonstrated moderate improvement in positive symptoms and aberrant salience, but maintained relatively high levels of dissociation and alexithymia throughout the observation period. Synthetic cannabinoid users showed the least improvement, with persistently elevated positive symptoms, minimal reduction in aberrant salience, and stable high levels of alexithymia across all time points. Notably, negative symptoms decreased in all groups over time, though they remained higher in non-users. These distinct recovery trajectories suggest differential effects of substance type on symptom persistence and treatment response in FEP.

4. Discussion

This paper presents an effort to compare three groups: non-users of cannabis, THC-users, and Synthetic cannabinoids-users. The comparison is conducted using the PANSS, the DES II, the ASI and the TAS-20. These assessments were carried out within each individual group and across all three groups, both at the onset of psychosis and during the follow-up period with antipsychotic treatment in real-life scenarios. One of the key innovations in this study is the focused assessment of the role of TAS-20 in the onset and progression of psychosis within the three groups of patients. Additionally, the study, offers a critical comparison between TAS-20 and ASI and its subscales. Our recruitment period spanned 2015–2024, during which significant changes occurred in cannabis availability and formulations in Italy. This period saw increasing potency of cannabis products and proliferation of new synthetic cannabinoid variants as manufacturers modified chemical structures to circumvent regulations. These evolving patterns of cannabis availability and potency may have introduced variability in our sample not fully captured in our analysis.

Across all psychopathological dimensions measured at three time points, our longitudinal analysis revealed consistent patterns: non-users showed the most robust improvement over time, natural cannabis users demonstrated intermediate recovery with persistent deficits in emotional processing, while synthetic cannabinoid users exhibited minimal improvement and maintained high levels of psychopathology throughout the observation period. These differential trajectories were particularly evident in positive symptoms, aberrant salience, and alexithymia, suggesting substance-specific effects on recovery processes and treatment response. Unlike previous cross-sectional research, our six-month follow-up design allows us to demonstrate for the first time the divergent recovery trajectories between these three distinct groups, particularly highlighting the persistence of alexithymia in cannabis users regardless of improvement in other symptom domains.

SCs exhibited more severe positive symptoms compared to NC users and non-users, consistent with literature (Ricci et al., 2021a; Martinotti et al., 2021b; Escelsior et al., 2021) and our previous research (Ricci et al., 2023, 2024). Importantly, our longitudinal data extend this finding by demonstrating that these differences persist throughout the six-month observation period despite antipsychotic treatment, with SCs users showing minimal symptom reduction compared to the other groups. This persistent symptom severity has significant clinical implications, suggesting that patients with SCs-induced psychosis may require more intensive treatment approaches, longer hospitalization, and careful monitorin (Van Amsterdam et al., 2015). Our study is the first to document the differential treatment response between SC and NC users during a standardized six-month antipsychotic regimen, providing clinicians with evidence-based expectations for recovery timelines in these distinct patient populations.

Negative psychotic symptoms decreased across all groups during the observation period but were more pronounced in NU than in NC and SCs consistent with prior findings (Welter et al., 2017; Ricci et al., 2021b; Kram et al., 2019). However, negative symptoms remained higher in non-users, especially compared to SCs users. This counterintuitive finding—that SCs users showed lower negative symptoms despite more severe positive symptoms—may be explained by two mechanisms: First, SCs-induced dopaminergic activation may selectively enhance positive symptoms while affecting mesocortical pathways associated with negative symptoms less. Second, the severity of positive symptoms might mask the recognition and assessment of co-occurring negative symptoms. **Difficulties in identifying emotions correlate with negative symptoms like emotional flattening and social withdrawal (Taylor et al., 1997). Gross (2002) showed that suppression as an emotional regulation strategy leads to reduced positive affect and poorer interpersonal functioning, fostering emotional and social withdrawal. Other studies

(Todarello et al., 2005) found no correlation between alexithymia and negative symptoms. However, Stanghellini and Ricca (1995) linked alexithymia to non-paranoid schizophrenia, suggesting that difficulty processing emotional states may predispose individuals to negative symptoms.** Our data contribute to this theoretical framework by demonstrating that this pattern persists over time, with SC users consistently showing this inverse relationship between positive and negative symptoms throughout the observation period, suggesting a distinct psychopathological profile rather than a transient phenomenon.

All groups showed reductions in total and subscale ASI scores over time. However, SCs users consistently had higher ASI scores, indicating increased aberrant salience (AS) and limited improvement with psychopharmacotherapy. This may result from SCs-induced dopaminergic hyperactivation, with mesolimbic dopaminergic hyperfunction driving maladaptive associative learning early in the illness (Kätzel et al., 2020; Millard et al., 2022). Antipsychotics appear to have limited efficacy in reversing these disruptions (Kätzel et al., 2020). Our study is the first to demonstrate the differential impact of natural versus synthetic cannabinoids on aberrant salience over time, with our data showing that SC users maintain significantly elevated ASI scores despite antipsychotic treatment, while NC users show intermediate improvement. No significant differences were observed between THC users and other groups, though some studies suggest generic THC users may experience increased AS. THC administration can disrupt salience processing in healthy individuals, resembling patterns seen in psychosis. Cannabis-induced psychotic symptoms correlate with AS, but this association is not consistent across all users, suggesting salience processing disruptions link cannabis use and psychosis (Bloomfield et al., 2016). The exaggerated attribution of meaning in AS amplifies the importance of neutral stimuli (Kapur et al., 2005). While therapy reduced this across all groups, SCs users had higher baseline ASI scores than NC and NU. Consistent with previous finding (Ricci et al., 2024), synthetic cannabinoids cause greater dopaminergic and opioid system dysregulation, contributing to heightened AS.

4.1. Alexithymia in cannabis-related psychosis

Alexithymia has been examined as a potential predictor of dissociative tendencies (Scigala et al., 2022) and is increasingly recognized as a significant factor in both substance use disorders and psychosis. Dissociation disrupts connections between affect, cognition, and behavior, influencing the development of alexithymia and the fragmentation of emotional, cognitive, and physiological components. Both dissociation and alexithymia are impairments in emotional perception, often serving as dysfunctional defense strategies against overwhelming affective states (Zdankiewicz-Ścigała and Scigala, 2018). Firstly, at baseline (T0), there was no significant difference in high levels of alexithymia across the different groups, suggesting that the three groups started with comparable levels and that high alexithymia levels are characteristic of psychotic onsets. This finding from our study challenges previous assumptions that cannabis users might begin with higher alexithymia levels, demonstrating instead that the onset of psychosis itself may be associated with elevated alexithymia regardless of substance use history. Indeed, alexithymia is usually considered a trait variable (in the sense of a stable deficit), although it is well-established that various circumstances, including substance use, can trigger or intensify it (Morie et al., 2016). In our study, we observed differential patterns of alexithymia across the three groups over time. There was a significant reduction in alexithymia levels among NU but a persistence of elevated levels in substance users, whether NC or SC users. This observation suggests an association between continued cannabis use and maintained alexithymia, though our study design cannot establish causality. The comparative patterns, however, indicate that substances may be related to poorer recovery of emotional processing capabilities, regardless of whether natural or synthetic cannabinoids are involved. Our longitudinal data provide the first evidence that alexithymia may be more state-dependent in non-cannabis-related psychosis, while remaining trait-like in cannabis users even after symptom remission, a distinction not previously established in the literature.

Our findings extend this theoretical model by demonstrating that the relationship between alexithymia and dissociation is particularly strong in cannabis users, with both NC and SC groups showing persistent elevations in both constructs compared to non-users, suggesting a specific cannabis-related disruption to emotional processing that persists despite treatment. In substance use disorder (SUD) patients, maladaptive defenses such as rationalization, projection, denial, and suppression are common, alongside immature mechanisms like acting out and isolation (Miller, 1985; Iwanicka et al., 2017). These defenses are strongly linked to addiction severity, dissociation, and alexithymia (Evren et al., 2012; Helmes et al., 2008). Research highlights a connection between early trauma and alexithymic traits in Alcohol Use Disorder (AUD), with dissociative tendencies frequently co-occurring (Craparo et al., 2014). Up to 50 % of AUD patients are alexithymic, reflecting challenges in identifying, expressing, and regulating emotions (Blaya et al., 2006). Chronic dissociation worsens emotional identification, while chemically induced dissociative states may temporarily enhance emotional access. Higher dissociative symptoms are observed in SUD patients compared to those with alcohol dependence alone, particularly in those using multiple substances (Schäfer et al., 2007; Karadag et al., 2005).

At present, no studies investigate the association between alexithymia, psychotic onset, and the use of cannabis (both natural and synthetic), particularly the potential role played by alexithymia in psychotic onsets among NU, NC users, and SC users. In SUD, alexithymia appears to predispose individuals to addiction, as it is associated with emotional dysregulation, immature defense mechanisms, and dissociation. High prevalence rates of alexithymia are reported among SUD patients (Parolin et al., 2018), with significant links to substance craving, disorder severity, socio-relational issues, and negative affectivity (Thorberg et al., 2011). Notably, 50 % of AUD patients are alexithymic (Blava et al. 2006), and AUD may reflect a dissociative reaction to difficulties in identifying, expressing, and regulating emotions (Craparo et al., 2014). Similarly, schizophrenia studies indicate that patients, especially with non-paranoid types, struggle with emotional awareness and expression (Salminen et al., 1999). However, confounding factors, such as severe symptoms or psychosis medication, might also limit emotional awareness (Taylor et al., 1997). Further research is needed to determine whether alexithymia is a cause or consequence of substance use. Alexithymia fosters emotional dysregulation and primitive defense mechanisms, driving substance use, while substance use—especially frequent or high-dose—induces symptoms like dissociation and psychosis, which hinder emotional accessibility and reinforce externally focused thinking.

By measuring both alexithymia and dissociation longitudinally in cannabis-related FEP, our study provides unique empirical evidence of their interrelated trajectories, showing for the first time that these constructs follow parallel recovery patterns, supporting the hypothesis that they may represent overlapping psychopathological processes particularly affected by cannabinoids. Individuals with higher alexithymia levels often adopt maladaptive strategies (e.g., emotion suppression) in stressful situations, leading to heightened arousal without changes in negative affect.

4.2. Alexithymia (TAS 20) and aberrant salience (ASI)

A novel aspect of this study is the exploration of correlations between alexithymia and aberrant salience using the TAS-20 and ASI scales. While no correlation was identified between the overall scales, specific associations were observed between two ASI subscales—"Feelings of Increased Significance" (FIS) and "Sense Sharpening" (SS)—and the TAS-20 across all groups. This is the first study to identify these specific correlations between alexithymia and aberrant salience subscales, providing new insights into how emotional processing difficulties may

relate to particular aspects of anomalous perceptual experiences in psychosis. FIS, which reflects an exaggerated attribution of significance to neutral stimuli, and SS, which denotes perceptual anomalies, represent prodromal psychotic experiences. These factors are phenomenologically characterized by a heightened sense of uncertainty and the attribution of novel meanings to otherwise neutral stimuli (Kapur et al., 2005). The elevated baseline alexithymia levels observed across all groups suggest that emotional processing impairments could be a potential risk factor for various psychiatric disorders, including somatization, schizophrenia, and psychosis in general (Taylor et al., 1997). Furthermore, the prodromal psychotic states captured by FIS and SS might make individuals less accessible to their own emotional states, expressions, and external interactions—hallmarks of alexithymia. Our findings highlight an association between these two psychopathological constructs across the three observation points, suggesting they may be related aspects of the psychotic experience. Our study reveals a previously undocumented fundamental connection between alexithymia and specific aberrant salience components that persists despite symptomatological variations. The correlations between alexithymia and particular ASI subscales remain consistent throughout the recovery process, indicating interconnected psychological mechanisms that evolve in parallel. While our observations provide insights into the evolution of these constructs over six months, future research with more frequent assessments and extended follow-up periods will be necessary to establish potential causal relationships and determine whether alexithymia functions as a risk factor, consequence, or maintaining element in cannabis-associated psychosis.

5. Limitations

This study has several limitations. The small sample size (n = 108), drawn from specific Italian regions, limits generalizability. We acknowledge that this represents a significant constraint when interpreting our findings. Despite our efforts to ensure internal validity, our results may not be directly applicable to different cultural, sociodemographic, or healthcare contexts outside Italy Self-reported measures, while robust, may be biased, particularly in acute psychosis. The study's observational design prevents causal conclusions about cannabis use, alexithymia, and psychotic symptoms. Specifically, our recruitment initially approached 153 potential participants, with a final sample of 108 (70.6 % participation rate), reflecting the challenges of studying this population. Methodological considerations include the exclusion of 22 individuals due to: Comorbid substance use disorders (n = 14); Significant medical conditions (n = 5); Intellectual disability (n = 3). Furthermore, the heterogeneity and potency of cannabis products, especially synthetic cannabinoids, were not fully accounted for, potentially influencing outcomes. The lack of follow-up beyond six months limits insight into long-term effects and symptom persistence. Regarding the Italian healthcare context, readers should consider that Italy provides universal healthcare access with integrated community-based mental health services. This may result in earlier intervention and more continuous care than in systems with different structures, potentially affecting recovery trajectories observed in our study.

Future research with larger, diverse samples and extended follow-up is needed to better understand the relationship between cannabis use and psychosis.

6. Conclusion

This study highlights the distinct neuropsychiatric impacts of natural cannabis and synthetic cannabinoids on psychotic symptoms, dissociation, aberrant salience, and alexithymia. Synthetic cannabinoids were associated with more severe and persistent positive symptoms, heightened aberrant salience, and limited alexithymia recovery compared to natural cannabis and non-users, emphasizing their greater neuropsychiatric risk and the need for tailored therapies. A key innovation lies in the longitudinal analysis of alexithymia and aberrant salience, revealing their significant interplay in shaping psychotic trajectories. Specific ASI and TAS-20 subscales emerged as early psychosis markers, deepening understanding of the underlying mechanisms. Alexithymia and dissociation were identified as critical factors in both the onset and persistence of psychosis, highlighting their dual role as risk markers and therapeutic targets. While antipsychotics improved symptoms, the findings stress the importance of addressing emotional dysregulation and salience processing, particularly in SC-induced psychosis. Future research should investigate the long-term trajectories of these constructs and their integration into personalized treatments to enhance outcomes for individuals with cannabis-related psychosis.

CRediT authorship contribution statement

Ricci Valerio: Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Di Muzio Ilenia:** Writing – original draft, Project administration, Data curation, Conceptualization. **Mancusi Gianluca:** Writing – original draft, Validation, Methodology. **Ceci Franca:** Writing – original draft, Project administration, Data curation, Conceptualization. **Ciavarella Maria Celeste:** Writing – original draft, Project administration, Data curation, Conceptualization. **Di Carlo Francesco:** Writing – original draft, Validation, Methodology. **Pettorruso Mauro:** Validation, Supervision, Methodology, Conceptualization. **Martinotti Giovanni:** Supervision, Conceptualization. **Maina Giuseppe:** Supervision, Conceptualization.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Altintas, M., Inanc, L., Oruc, G., et al., 2016. Clinical characteristics of synthetic cannabinoid-induced psychosis in relation to schizophrenia: a single-center cross-sectional analysis of concurrently hospitalized patients. Neuropsychiatric Dis. Treat. 12, 1893–1900. https://doi.org/10.2147/NDT.S107622.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual. American Psychiatric Association, Arlington.

Anglin, D.M., Tikhonov, A.A., Tayler, R., et al., 2021. The role of aberrant salience in the association between cannabis use frequency and psychotic experiences among racial and ethnic minoritized youth. Schizophr. Res. 238, 36–43. https://doi.org/10.1016/j.schres.2021.09.016.

Bagby, R.M., Parker, J.D., Taylor, G.J., 1994. The twenty-item Toronto Alexithymia scale—I. Item selection and cross-validation of the factor structure. J. Psychosom. Res. 38 (1), 23–32. https://doi.org/10.1016/0022-3999(94)90005-1.

Baler, R.D., Volkow, N.D., 2011. Addiction as a systems failure: focus on adolescence and smoking. J. Am. Acad. Child Adolesc. Psychiatry 50 (4), 329–339. https://doi.org/10.1016/j.jaac.2010.12.008.

Bernstein, E.M., Putnam, F.W., 1986. Development, reliability, and validity of a dissociation scale. J. Nerv. Ment. Dis. 174, 727–735. https://doi.org/10.1097/00005053-198612000-00004.

Blaya, C., Dornelles, M., Blaya, R., et al., 2006. Do defense mechanisms vary according to the psychiatric disorder? Brazilian Journal of Psychiatry 28 (3), 179–183. https://doi.org/10.1590/s1516-44462006000300007.

Bloomfield, M.A., Mouchlianitis, E., Morgan, C.J., et al., 2016. Salience attribution and its relationship to cannabis-induced psychotic symptoms. Psychol. Med. 46 (16), 3383–3395. https://doi.org/10.1017/S0033291716002051.

Cicero, D.C., Kerns, J.G., McCarthy, D.M., 2010. The aberrant salience inventory: a new measure of psychosis proneness. Psychol. Assess. 22, 688–701. https://doi.org/10.1037/a0019913.

Craparo, G., Ardino, V., Gori, A., Caretti, V., 2014. The relationships between early trauma, dissociation, and alexithymia in alcohol addiction. Psychiatry Investigation 11 (3), 330–335. https://doi.org/10.4306/pi.2014.11.3.330.

Cruise, K.E., Becerra, R., 2018. Alexithymia and problematic alcohol use: a critical update. Addict. Behav. 77, 232–246. https://doi.org/10.1016/j.addbeh.2017.09.025.
D'Souza, D.C., Sewell, R.A., Ranganathan, M., 2009. Cannabis and psychosis/schizophrenia: human studies. Eur Arch Psychiatry Clin Neurosci 259, 413–431. https://doi.org/10.1007/s00406-009-0024-2.
Elsohly, M.A., Gul, W., Wanas, A.S., et al., 2014. Synthetic cannabinoids: analysis and metabolites. Life Sci. 97, 78–90. https://doi.org/10.1016/j.lfs.2013.12.212.
EMCDDA, 2023. European drug report 2023: trend and developments [Internet]. Retrieved January 15, 2025, from. https://www.emcdda.europa.eu/publications/european-drug-report/2023_en.
Escelsior, A., Murri, M.B., Corsini, G.P., et al., 2021. Cannabinoid use and self-injurious behaviours: a systematic review and meta-analysis. J. Affect. Disord. 278, 85–98. https://doi.org/10.1016/j.jad.2020.09.020.
Evren, C., Cagil, D., Ulku, M., et al., 2012. Relationship between defense styles, alexithymia, and personality in alcohol-dependent inpatients. Compr. Psychiatry 53 (6), 860–867. https://doi.org/10.1016/j.comppsych.2012.01.002.
Fossati, A., Acquarini, E., Feeney, J.A., et al., 2009. Alexithymia and attachment insecurities in impulsive aggression. Attach Hum Dev 11 (2), 165–182. https://doi.org/10.1080/14616730802625235.
Gross, J.J., 2002. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 39, 281–291.
Helmes, E., McNeill, P.D., Holden, R.R., et al., 2008. The construct of alexithymia: associations with defense mechanisms. J. Clin. Psychol. 64 (3), 318–331. https://doi.org/10.1002/jclp.20461.
Hinckley, J.D., Mikulich-Gilbertson, S.K., He, J.P., et al., 2023. Cannabis use is associated with depression severity and suicidality in the national comorbidity survey−Adolescent supplement. JAACAP Open 1 (1), 24–35. https://doi.org/10.1016/j.jaacop.2023.02.002.
Hindson, S.A., Andrews, R.C., Danson, M.J., et al., 2023. Synthetic cannabinoid receptor agonists are monoamine oxidase-a selective inhibitors. FEBS J. 290, 3243–3257. https://doi.org/10.1111/febs.16741.
Iwanicka, K., Gerhant, A., Olajossy, M., 2017. Psychopathological symptoms, defense mechanisms, and time perspectives among subjects with alcohol dependence (AD) presenting different patterns of coping with stress. PeerJ 5, e3576. https://doi.org/10.7717/peerj.3576.
Kapur, S., Mizrahi, R., Li, M., 2005. From dopamine to salience to psychosis—linking biology, pharmacology, and phenomenology of psychosis. Schizophr. Res. 79 (1), 59–68. https://doi.org/10.1016/j.schres.2005.01.003.
Karadag, F., Sar, V., Tamar-Gurol, D., et al., 2005. Dissociative disorders among inpatients with drug or alcohol dependency. J. Clin. Psychiatry 66, 1247–1253.
Kätzel, D., Wolff, A.R., Bygrave, A.M., et al., 2020. Hippocampal hyperactivity as a druggable circuit-level origin of aberrant salience in schizophrenia. Front. Pharmacol. 11, 486811. https://doi.org/10.3389/fphar.2020.486811.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.
Kram, H., Mokrysz, C., Curran, H.V., 2019. What are the psychological effects of using synthetic cannabinoids? J. Psychopharmacol. 33, 271–283. https://doi.org/10.1177/0269881119826592.
Lane, R.D., Sechrest, L., Riedel, R., 1998. Sociodemographic correlates of alexithymia. Compr. Psychiatry 39, 377–385.
Martinotti, G., De, R.L., Vannini, C., Schifano, F., et al., 2021a. Substance-related exogenous psychosis: a postmodern syndrome. CNS Spectr. 26, 84–91. https://doi.org/10.1017/S1092852920001479.
Martinotti, G., Del, V.C.M., Cordoba, A.G., Tubau, L.A., et al., 2021b. Club drugs and psychiatric sequelae: an issue of vulnerability and previous psychiatric history. Int. J. Environ. Res. Publ. Health 18, 6944. https://doi.org/10.3390/ijerph18136944.
Mattila, A.K., Poutanen, O., Koivisto, A.M., et al., 2007. Alexithymia and life satisfaction in primary healthcare patients. Psychosomatics 48 (6), 523–529. https://doi.org/10.1176/appi.psy.48.6.523.
Millard, S.J., Bearden, C.E., Karlsgodt, K.H., et al., 2022. The prediction-error hypothesis of schizophrenia: new data point to circuit-specific changes in dopamine activity. Neuropsychopharmacology 47 (3), 628–640. https://doi.org/10.1038/s41386-021-01188-y.
Miller, W.R., 1985. Motivation for treatment: a review with special emphasis on alcoholism. J. Clin. Psychol. 98 (1), 84–107. https://doi.org/10.1037/0033-2909.98.1.84.
Morie, K.P., Yip, S.W., Nich, C., Hunkele, K., Carroll, K.M., Potenza, M.N., 2016. Alexithymia and addiction: a review and preliminary data suggesting neurobiological links to reward/loss processing. Current addiction reports 3 (2), 239–248. https://doi.org/10.1007/s40429-016-0097-8.
Papanti, D., Schifano, F., Botteon, G., et al., 2013. "Spiceophrenia": a systematic overview of "spice"-related psychopathological issues and a case report. Hum. Psychopharmacol. 28, 379–389. https://doi.org/10.1002/hup.2312.
Parolin, M., Miscioscia, M., De Carli, P., et al., 2018. Alexithymia in young adults with substance use disorders: critical issues about specificity and treatment predictivity. Front. Psychol. 9, 645. https://doi.org/10.3389/fpsyg.2018.00645.
Patti, A., Santarelli, G., D'Anna, G., et al., 2022. Aberrant salience among young healthy postgraduate university students: the role of cannabis use, psychotic-like experiences, and personality. Psychopathology 55, 116–122. https://doi.org/10.1159/000520331.
Poletti, M., Pelizza, L., Azzali, S., et al., 2022. Subjective experience of aberrant salience in young people at ultra-high risk (UHR) for psychosis: a cross-sectional study. Nord. J. Psychiatr. 76, 129–137. https://doi.org/10.1080/08039488.2021.1942547.
Pugliese, V., de Filippis, R., Aloi, M., et al., 2022. Aberrant salience correlates with psychotic dimensions in outpatients with schizophrenia spectrum disorders. Ann. Gen. Psychiatr. 21, 25. https://doi.org/10.1186/s12991-022-00402-5.
Quattrone, D., Ferraro, L., Tripoli, G., et al., 2021. Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case–control study. Psychol. Med. 51, 1329–1337. https://doi.org/10.1017/S0033291720000082.
Ransing, R., de la Rosa, P.A., Pereira-Sanchez, V., et al., 2021. Current state of cannabis use, policies, and research across sixteen countries: cross-country comparisons and international perspectives. Trends Psychiatry Psychother 44, e20210263. https://doi.org/10.47626/2237-6089-2021-0263.
Reed, S.I., 2008. First-episode psychosis: a literature review. Int. J. Ment. Health Nurs. 17, 85–91. https://doi.org/10.1111/j.1447-0349.2008.00515.x.
Ricci, V., Martinotti, G., Ceci, F., et al., 2021a. Duration of untreated disorder and cannabis use: an observational study on a cohort of young Italian patients experiencing psychotic experiences and dissociative symptoms. Int. J. Environ. Res. Publ. Health 18 (23), 12632. https://doi.org/10.3390/ijerph182312632.
Ricci, V., Ceci, F., Di Carlo, F., et al., 2021b. Cannabis use disorder and dissociation: a report from a prospective first-episode psychosis study. Drug Alcohol Depend. 229, 109118. https://doi.org/10.1016/j.drugalcdep.2021.109118.
Ricci, V., Ceci, F., Di Carlo, F., et al., 2023. First episode psychosis with and without the use of cannabis and synthetic cannabinoids: psychopathology, global functioning and suicidal ideation and antipsychotic effectiveness. Psychiatry Res. 320, 115053. https://doi.org/10.1016/j.psychres.2023.115053.
Ricci, V., Di Muzio, I., Ceci, F., et al., 2024. Aberrant salience in cannabis-induced psychosis: a comparative study. Front Psychiatry 14, 1343884. https://doi.org/10.3389/fpsyt.2023.1343884.
Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Rev. 18 (3), 247–291.
Salminen, J.K., Saarijarvi, S., Aarela, E., et al., 1999. Prevalence of alexithymia and its association with sociodemographic variables in the general population of Finland. J. Psychosom. Res. 46, 75–82.
Saunders, J.B., Sellman, J.D., 2003. A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. Drug Alcohol Rev. 22, 309–315. https://doi.org/10.1080/0959523031000154454.
Schäfer, I., Reininghaus, U., Langeland, W., et al., 2007. Dissociative symptoms in alcohol-dependent patients: associations with childhood trauma and substance abuse characteristics. Compr. Psychiatry 48 (6), 539–545. https://doi.org/10.1016/j.comppsych.2007.05.013.
Scherbaum, N., Schifano, F., Bonnet, U., 2017. New psychoactive substances (NPS) - a challenge for the addiction treatment services. Pharmacopsychiatry 50 (3), 116–122. https://doi.org/10.1055/s-0043-102059.
Schimmelmann, B.G., Conus, P., Cotton, et al., 2011. Cannabis use disorder and age at onset of psychosis: a study in first-episode patients. Schizophr. Res. 129, 52–56. https://doi.org/10.1016/j.schres.2011.03.023.
Schoeler, T., Petros, N., Forti, M.D., et al., 2017. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. Lancet Psychiatry 4, 627–633. https://doi.org/10.1016/S2215-0366(17)30233-X.
Scigala, D.K., Fabris, M.A., Badenes-Ribera, L., et al., 2022. Alexithymia and adult attachment: investigating the mediating role of fear of intimacy and negative mood regulation expectancies. Psychol. Rep. 125 (4), 1896–1914. https://doi.org/10.1177/00332941211010252.
Seddon, J.L., Birchwood, M., Copello, A., et al., 2016. Cannabis use is associated with increased psychotic symptoms and poorer psychosocial functioning in first-episode psychosis: a report from the UK national EDEN study. Schizophr. Bull. 42, 619–625. https://doi.org/10.1093/schbul/sbv154.
Sherif, M.A., Cortes-Briones, J.A., Ranganathan, M., et al., 2018. Cannabinoid-glutamate interactions and neural oscillations: implications for psychosis. Eur. J. Neurosci. 48, 2890–2902. https://doi.org/10.1111/ejn.13800.
Sifneos, P.E., 1973. The prevalence of 'alexithymia' characteristics in psychosomatic patients. Psychother. Psychosom. 22 (2), 255–262. https://doi.org/10.1159/000286529.
Skinner, H.A., 1982. The drug abuse screening test. Addict. Behav. 7 (4), 363–371. https://doi.org/10.1016/0306-4603(82)90005-3.
Stanghellini, G., Ricca, V., 1995. Alexithymia and schizophrenias. Psychopathology 28 (5), 263–272. https://doi.org/10.1159/000284937.
Taylor, G.J., Bagby, R.M., Parker, J.D.A., 1997. Disorders of Affect Regulation: Alexithymia in Medical and Psychiatric Illness. Cambridge University Press, Cambridge.
Thorberg, F.A., Young, R.M., Sullivan, K.A., Lyvers, M., 2009. Alexithymia and alcohol use disorders: a critical review. Addict. Behav. 34 (3), 237–245. https://doi.org/10.1016/j.addbeh.2008.10.016.
Thorberg, F.A., Young, R.M., Sullivan, K.A., et al., 2011. Parental bonding and alexithymia: a meta-analysis. Eur Psychiatry 26 (3), 187–193. https://doi.org/10.1016/j.eurpsy.2010.09.010.
Todarello, O., Porcelli, P., Grilletti, F., Bellomo, A., 2005. Is alexithymia related to negative symptoms of schizophrenia? A preliminary longitudinal study. Psychopathology 38 (6), 310–314.
van Amsterdam, J., Brunt, T., van den Brink, W., 2015. The adverse health effects of synthetic cannabinoids with emphasis on psychosis-like effects. J. Psychopharmacol. 29, 254–263. https://doi.org/10.1177/0269881114565142.

Welter, S., Lücke, C., Lam, A.P., et al., 2017. Synthetic cannabinoid use in a psychiatric patient population: a pilot study. Eur Addict Res 23, 182–193. https://doi.org/10.1159/000479554.

Zdankiewicz-Ścigała, E., Ścigała, D.K., 2018. Relationship between attachment style in adulthood, alexithymia, and dissociation in alcohol use disorder inpatients: a mediational model. Front. Psychol. 9, 2039. https://doi.org/10.3389/fpsyg.2018.02039.

Zuckerman, M., Kuhlman, D.M., 2000. Personality and risk-taking: common biosocial factors. J. Pers. 68 (6), 999–1029. https://doi.org/10.1111/1467-6494.00124.