It is illegal to post this copyrighted PDF on any website. Age at the Time of Exposure to Trauma Modulates the Psychopathological Profile in Patients With Early Psychosis

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ABSTRACT

Objective: To examine the potential differential impact of childhood trauma, according to the age at the time of exposure, on the psychopathological profile of patients with early psychosis treated in a specialized 3-year program during the early phase of the disease.

Methods: 196 subjects with early psychosis aged 18–35 years were followed up prospectively over 36 months of treatment between 2004 and 2010. Patients who had faced at least 1 experience of abuse (physical, sexual, or emotional) or neglect (physical or emotional) were classified according to age at the time of the first exposure (early trauma: before 12 years of age; late trauma: from age 12 through 16 years) and then compared with unexposed patients (nontrauma). The level of symptoms was assessed using the Positive and Negative Syndrome Scale, the Young Mania Rating Scale, and the Montgomery-Asberg Depression Rating Scale.

Results: Exposure to 1 or more forms of trauma before 16 years of age was present in 31.63% of patients. Comparisons over the 3 years of treatment with the nontrauma patients revealed that (1) patients with early trauma showed consistently higher levels of positive (P=.006), depressive (P=.001), manic (P=.006), and negative (P=.029) symptoms and (2) patients with late trauma showed only more negative symptoms (P=.029).

Conclusions: These results suggest that the age at the time of exposure to trauma has a modulating effect on symptoms in patients with early psychosis. Various biological and psychological hypotheses can be proposed to explain this observation, and they need to be investigated in an experimental setting in order to develop therapeutic avenues.

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*Corresponding author: Luis Alameda, MD, Treatment and Early Intervention in Psychosis Program (TIPP), Rue de Caroline 2, Lausanne, 1003, Switzerland (laluisalameda@gmail.com). **E** xposure to trauma during childhood appears to have an impact on the risk of developing psychosis,^{1,2} and research performed on patients suffering from the disease has shown that those exposed to childhood trauma, when compared to their nonexposed counterparts, show some specific demographic, clinical, and functional characteristics.³⁻⁵ Substantial research has shown a link between exposure to childhood trauma and higher levels of severity in hallucinations and delusions, both in chronic⁶⁻⁸ and in first-episode psychosis^{9,10} patients. The link between negative symptoms intensity and childhood trauma is less clear; an extensive review on this topic did not find any association,⁶ while later studies in first-episode psychosis revealed either no association^{9,11,12} or an association only in the case of certain specific types of trauma such as emotional neglect.¹⁰ Intriguingly, articles^{13,14} in the field of trauma rarely address the issue of negative symptoms.

Some studies^{8,15} have shown that psychotic patients exposed to childhood trauma present more depressive symptoms when compared with nonexposed patients. Concerning manic symptoms, a recent study¹⁶ in a population of first-episode psychotic mania has shown that exposed patients present more manic symptoms when compared with their nonexposed counterparts. Despite this evidence linking childhood trauma to some clinical manifestations in psychosis, none of these studies have considered the age at the time of exposure to childhood trauma.

There are suggestions in the literature that age at the time of exposure may modulate the impact of trauma in later life. One study¹⁷ of 585 preschool boys and girls recruited as a community sample has shown that those who were exposed before the age of 5 years presented more adjustment problems in early adolescence than those exposed at a later age. Another study¹⁸ of 90 frequent attenders of general practitioners showed that reactivity to emotional stress was greater in subjects exposed to childhood trauma before the age of 10 years. A recent study³ from our group conducted on a sample of 225 patients with early psychosis showed that patients exposed to sexual and/or physical abuse before 12 years of age maintained a poorer functional level than nonexposed patients throughout the entire 3 years of follow-up, while this was not the case for those exposed at a later age. These findings are in line with prior neurobiological evidence that trauma at a younger age has more intense and long-lasting consequences at the brain level than trauma occurring later.^{19,20}

Considering the lack of a clear understanding of the link between the age at the time of exposure to childhood trauma and its consequences, we planned the current study to examine, in a sample of 196 early psychosis patients treated in a specialized program for 3 years, if age at the time of exposure to trauma modulates the impact of childhood trauma on the psychopathological profile of patients during the early phase of the disease. We hypothesized that patients

Alameda et al It is illegal to post this copyrighted PDF on any website purposes. Therefore, every patient who takes part in TIPP

- Childhood trauma is linked to an increased risk for psychosis and symptom severity. Our data confirm that exposure to trauma is highly prevalent in early psychosis samples and that age at the time of exposure to trauma modulates its impact on clinical presentation and outcome.
- Early intervention programs should systematically evaluate the exposure to life stressors and the age at time of exposure; specific interventions and efforts should be undertaken addressing clinical, emotional, cognitive, and interpersonal consequences of severe trauma, particularly when occurring prior to 12 years of age.
- The different impact of trauma on symptom dimensions, depending on age at the time of exposure, may have a neurobiological substrate, and further research is needed to explore the underlying mechanisms.

exposed to traumatic experiences before 12 years of age would suffer from more severe and long-lasting symptoms than nontraumatized patients, while this would not be the case for patients exposed at a later age.

METHODS

Procedure and Subjects

The Treatment and Early Intervention in Psychosis Program (TIPP) is a specialized early psychosis program that was launched in 2004 at the Department of Psychiatry of Lausanne University Hospital in Lausanne, Switzerland.^{21,22} Entry criteria to the program are (1) age between 18 and 35 years; (2) residing in the catchment area (Lausanne and its surroundings; population about 300,000 persons); and (3) meeting threshold criteria for psychosis, as defined by the Psychosis Threshold subscale of the Comprehensive Assessment of At-Risk Mental States (CAARMS)²³ scale. Patients are referred to other treatment programs if they have been taking antipsychotic medication for more than a total of 6 months, have psychosis related to intoxication or organic brain disease, or have an intelligence quotient below 70.

A specially designed questionnaire (available from the corresponding author upon request) is completed for all patients enrolled in the program by case managers who have up to 100 contacts with patients during the 3 years of treatment. It assesses demographic characteristics, past medical history, and exposure to life events, as well as symptoms and functioning. It is completed on the basis of information gathered from patients and their family over the first few weeks of treatment and can be updated during follow-up if new information emerges. Follow-up assessments, exploring various aspects of treatment and comorbidities, as well as evolution of psychopathology and functional level, are conducted by a research psychologist and by case managers after 2, 6, 12, 18, 24, 30, and 36 months of treatment.

The Research and Ethics Committee of the Faculty of Biology and Medicine of Lausanne University, Lausanne, Switzerland, granted access to TIPP clinical data for research purposes. Therefore, every patient who takes part in TIPP automatically participates in this study, without exception. This is a prospective study based on the 240 patients who had been enrolled in the program and who had been in treatment for 36 months. The current study was developed during 2014.

Diagnostic Assessment

Diagnosis is the result of an expert consensus and is based on the following elements: (1) diagnosis reported by a treating psychiatrist in all medical documents and at the end of any hospitalization and (2) longitudinal assessment by a clinical case manager during the 3 years of treatment. The consensus diagnosis procedure is performed by a senior psychiatrist and the senior psychologist in charge of scale-based assessment during the treatment period; they both review the entire file once after 18 months and again after 36 months, or at the end of treatment, and conduct a diagnostic process based on *DSM-IV* criteria,²⁴ discussing any unclear issue with the clinical case manager.

Assessment of History of Past Trauma

Clinicians at TIPP are trained to conduct an extensive assessment of patients, including evaluation of exposure to traumatic life events. Case managers meet patients frequently over the treatment period, which provides the framework to establish a trusting relationship, whereby extensive knowledge of patients' history can be gathered. If patients agree, information can also be completed with family. In the case of inconsistency between the patient's report and the family report or doubt about the exposure to trauma or the age at the time of exposure, patients were not included in the study.

Case managers complete a table (available from the corresponding author upon request) during the patients' 3 years of treatment, in which exposure to traumatic life events can be recorded as follows: (1) type of traumatic life event, rated as present or absent (sexual abuse, physical abuse, emotional and physical neglect, emotional abuse, among others); (2) time of trauma occurrence in relation to psychosis stage (during the premorbid phase, during the prodromal phase, or after onset of psychosis); (3) age at the time of first exposure to each of the traumas that occurred; and (4) single or repeated exposure to each of the traumas that occurred. Considering that the clinicians who assessed exposure to life events did not rate the subjective perception of severity of the different forms of stressful events, patients were considered as traumatized if they had been exposed to at least 1 experience of abuse (physical, sexual, or emotional) or neglect (physical or emotional), since such events would undoubtedly be considered as highly traumatizing by anyone and have been shown to be associated with risk for psychosis^{1,25} and more severe symptoms in psychotic samples.^{4,9} Sexual abuse refers to sexual molestation and/or rape. Physical abuse refers to physical attack or assault or being repetitively beaten by parents, relatives, or caregivers. Emotional abuse was

It is illegal to post this copy defined as verbal assaults on a child's sense of worth or wellbeing or any humiliating or demeaning behavior directed toward a child by an adult or older person. *Physical neglect* was defined as the failure of caretakers to provide for a child's basic physical needs, including food, shelter, clothing, safety, and health care. *Emotional neglect* was defined as the failure of caretakers to meet children's basic emotional and psychological needs, including love, belonging, nurturance, and support.²⁶

Age at the time of first exposure was categorized as follows: (1) early trauma refers to exposure from birth through 11 years of age, according to conventions applied elsewhere,^{3,27-29} and (2) late trauma refers to exposure from age 12 years through 16 years. Patients who were exposed to trauma after 16 years of age were excluded from this study, according to other studies,¹³ considering they may already have been in the prodromal phase of their first psychotic episode.

Level of Psychopathology

The level of positive and negative symptoms was assessed using the total score of the positive and negative components of the Positive and Negative Syndrome Scale (PANSS).^{30,31} Depressive symptoms were assessed using the total score of the Montgomery-Asberg Depression Rating Scale (MADRS).³² Manic symptoms were assessed using the total score of the Young Mania Rating Scale (YMRS).³³

Statistical Analysis

Comparisons in terms of demographic and baseline characteristics between nontrauma versus trauma (all exposed patients) and early-trauma versus late-trauma were performed with planned contrasts for 1-way independent analysis of variance for continuous variables and Fisher exact test for categorical variables.

Differences between groups in terms of psychopathology during the follow-up were estimated using a 2-level regression model in order to take the longitudinal structure of the data into account. All the observations throughout the follow-up assessment (2, 6, 12, 18, 24, 30, and 36 months after entry in TIPP) were considered. Trauma category (early and late) and covariates (age, sex, and socioeconomic level; socioeconomic status [SES] according to Chandola et al³⁴) were entered as predictors in the model. Random intercept models and random intercept and slope alternatives were selected using a likelihood ratio test, which allowed us to verify whether there were significant interindividual differences in the rate of change over time for each outcome (PANSS positive, PANSS negative, MADRS, and YMRS scores).

RESULTS

Patient Sample

Of the first 240 patients consecutively admitted to TIPP between 2004 and 2010, 44 patients were excluded from the study for the following reasons: (1) age at exposure to trauma was not available or there was doubt about the

exact age when trauma occurred (n=2); (2) first exposure to trauma occurred during their prodromal phase (n=4), after psychosis onset (n=4), or after age 16 years (n=3); and (3) they could not be approached by the psychologist for psychopathological evaluation (n=31). Therefore, data on 196 patients were analyzed. Within the 3 years of follow-up, each patient was assessed a mean 3.94 times for PANSS, 3.31 times for MADRS, and 3.76 times for YMRS. No differences in terms of age, gender, socioeconomic status, or diagnostic group were observed between the 196 patients who took part in the study and the 44 who did not. We found that excluded patients had a poorer level of functioning at baseline as measured with the Global Assessment of Functioning scale³⁵ (P=.032) and the Social and Occupational Functioning Assessment Scale³⁵ (P=.013), compared to included patients (Supplementary eTable 1; available at PSYCHIATRIST.COM).

Rates of Trauma and Demographic Characteristics

The diagnostic breakdown and baseline and demographic characteristics of the sample are described in Table 1. Among the 196 patients, 62 (31.63%) had a history of trauma. Within the trauma group, 44 (71%) had been exposed before age 12 years (early trauma) and 18 (29%) from age 12 through 16 years (late trauma). There were no differences in terms of diagnostic distribution or demographic and baseline characteristics, either between exposed and nonexposed patients or between those exposed early and late.

Overall Level of Symptoms in Relation to Exposure to Trauma During Childhood and Adolescence

While patients showed individual differences in their rate of change over time for depressive, positive, and negative symptoms, trauma had no significant effect on the slope parameter (ie, trauma category [early or late] could not explain or predict such variation). Results are reported in Table 2 and are illustrated in Figure 1 (1A for PANSS positive, 1B for PANSS negative, 1C for MADRS, and 1D for YMRS scores). Patients exposed early to trauma showed more positive (β = 1.75; *P* = .006), negative (β = 1.81; *P* = .029), depressive (β = 4.43; *P* = .001), and manic (β = 1.96; *P* = .006) symptoms overall, as compared to nonexposed patients. Patients exposed later to trauma showed only more negative symptoms (β = 2.72; *P* = .021) overall, as compared to nonexposed patients.

DISCUSSION

The current study demonstrates, in a sample of patients with early psychosis followed up prospectively, that the presence of a history of exposure to childhood trauma predicts different aspects of psychopathology, depending on the age at the time of exposure. The impact of childhood trauma on positive, depressive, and manic symptoms varies according to the age at the time of occurrence, while this is not the case for the negative symptoms. Indeed, when compared to nonexposed patients, those exposed before 12 years of age displayed higher levels of positive, depressive, Table 1. Demographic and Baseline Factors Related to Early or Late Exposure to Trauma^a

					Nontrauma	Early Trauma
					VS	VS
	Total	Nontrauma	Early Trauma	Late Trauma	Trauma	Late Trauma
	(N = 196)	(n = 134)	(n=44)	(n = 18)	(P Value)	(P Value)
Age, mean (SD), y	24.06 (4.82)	23.77 (4.85)	24.39 (4.51)	25.44 (5.35)	.150	.434
Sex, % (n), male	70.9 (139)	75.4 (101)	65.9 (29)	50.0 (9)	.062	.265
SES, % (n)						
Low	15.3 (30)	16.4 (22)	15.9 (7)	5.6 (1)	.781	.260
Intermediate	48.5 (95)	47.0 (63)	54.5 (24)	44.4 (8)		
High	36.2 (71)	36.6 (49)	29.5 (13)	50.0 (9)		
GAF baseline, mean (SD)	36.31 (15.42)	36.61 (15.10)	37.23 (16.60)	32.28 (15.17)	.477	.262
SOFAS baseline, mean (SD)	39.43 (15.81)	39.94 (15.73)	38.90 (15.62)	37.00 (17.42)	.453	.672
Diagnostic, % (n)						
Schizophrenia	60.2 (118)	59.7 (80)	59.1 (26)	66.7 (12)	.727	.104
Schizophreniform/BPE	11.2 (22)	12.7 (17)	11.4 (5)	0.0 (0)		
Schizoaffective disorder	9.2 (18)	8.2 (11)	9.1 (4)	16.7 (3)		
Major depression ^b	4.6 (9)	3.7 (5)	9.1 (4)	0.0 (0)		
Bipolar disorder	5.6 (11)	6.7 (9)	0.0 (0)	11.1 (2)		
Others	9.2 (18)	9.0 (12)	11.4 (5)	5.6 (1)		

^aAnalyses between nontrauma versus trauma and early trauma versus late trauma were performed with planned contrasts for 1-way independent analysis of variance for continuous variables and Fisher exact test for categorical variables. ^bWith psychotic features.

Abbreviations: BPE = brief psychotic episode, GAF = Global Assessment of Functioning, SES = socioeconomic status, SOFAS = Social and Occupational Functioning Assessment Scale.

and manic symptoms over the 3 years of treatment, while those exposed at a later age did not. While confirming previous findings that patients with early psychosis who were exposed to childhood trauma have higher levels of positive,^{9,10} depressive,^{8,15} and manic symptoms¹⁶ than do nonexposed patients,¹³ our data show that this is true only for those patients exposed at an earlier age.

A second finding is that whatever the age at the time of occurrence, childhood trauma is linked to durably higher levels of negative symptoms in early psychosis patients, a finding not reported in previous studies.^{6,9,11,12} It is probable that negative symptoms are more difficult to observe when positive symptoms are more predominant; this could explain why cross-sectional studies in early psychosis have often reported no association between exposure to childhood trauma and negative symptoms.^{9,11,12} These findings highlight the importance of conducting longitudinal studies that examine the long-term evolution of symptoms at different time points.

The difference between early versus late trauma in relation to the various symptom domains needs to be further explored. One explanation could be found at the neurobiological level. Stress-sensitive structures, such as the hippocampus, prefrontal cortex, or corpus callosum, have been shown to be altered in persons exposed to trauma³⁶ and displayed various timing patterns of neurodevelopment during the life span.^{19,37} It has been suggested that there may be different sensitive periods when persons are maximally susceptible to the effects of stress, prior to their final maturation during the period of enhanced plasticity.¹⁹ While the hippocampus volume reductions in adulthood were maximal in women exposed to trauma between 3 and 5 years old, alterations of the corpus callosum were at the maximum when maltreatment occurred at 9 and 10 years of age, and alterations in the prefrontal cortex were maximal when trauma occurred at ages 14-16 years.^{36,38}

Table 2. Level of Symptoms of Patients Exposed to Early and Late Trauma Compared With the Nonexposed Group Across All 3 Years of Follow-Up^a

	E	arly Trau	ma	Late Trauma		
Clinical Domain	β ^b	SE	P Value	β ^b	SE	P Value
PANSS positive	1.755	0.641	.006	1.429	0.913	.117
PANSS negative	1.811	0.829	.029	2.727	1.182	.021
MADRS	4.435	1.307	.001	1.054	2.039	.605
YMRS	1.965	0.711	.006	1.032	1.008	.306

^aAll results are adjusted by age, sex, and socioeconomic status. Boldface indicates significance.

^bEstimates.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SE = standard error, YMRS = Young Mania Rating Scale.

Furthermore, gene-environment experimental models also highlighted childhood/peripuberty as critical periods of high vulnerability for environmental adverse insults; indeed, in a genetic schizophrenia model of oxidative stress,³⁹ additional oxidative challenges in juvenile and peripubertal ages, but not in young adulthood, led to severe and permanent microcircuit alterations in the prefrontal cortex, involving parvalbumin interneurons, neural synchronization, and cognition⁴⁰ (reviewed in Do et al⁴¹ and Steullet et al⁴²). Abnormal redox control in adolescence also led to alterations in the myelination processes in the prefrontal cortex.43 Thus, it has been hypothesized that the timing of environmental insults levied upon an (at-risk) individual during development may determine which brain regions and circuits are structurally and functionally affected, and this, in combination with specific genetic vulnerability, could differentially affect circuit connectivity associated with positive, negative, manic, depressive, or cognitive symptoms.⁴² Therefore, we speculate that insults occurring at early ages may induce a global and long-lasting impairment on neural connectivity, leading to a mixture of positive, negative, depressive, and manic symptoms, while

It is illegal to post this copyrighted PDF on any website Figure 1. Psychopathology Scores Over 36 Months: Comparisons Between Early- or Late-Trauma Patients and Nontrauma

Patients





later trauma may have an impact on circuits involved in the negative symptoms. Our results could also suggest that the psychological impact of trauma may differ depending on the age at the time of occurrence. Trauma at a very early age may have a deep and long-lasting impact on a wide range of psychological functions, while later occurrence may have a stronger impact on domains such as self-confidence, selfesteem, or interpersonal interactions, dimensions that may be captured by the negative symptoms of the PANSS.

The present investigation has some important clinical implications. Our results suggest that patients exposed to trauma early in their lives could represent a subgroup of patients suffering from a more severe form of disease, characterized by higher levels of severity in symptoms and long-term social and vocational disabilities,³ which limit their chances of recovery. Treatment offered at TIPP may not be sufficient for these patients, who could additionally benefit from a more specific approach addressing clinical,

emotional, cognitive, and interpersonal consequences of severe trauma. Some authors have undertaken several efforts to apply specific psychotherapeutic interventions to traumatized patients with severe mental illness, some of which consist of a multicomponent cognitivebehavioral intervention,⁴⁴ with programs including group psychoeducation, reframing, and problem solving^{45,46} or treatments focused on establishing a therapeutic alliance with the patient and then assisting them to engage in increasingly complex acts of metacognition.⁴⁷ In summary, additional treatment efforts should be undertaken to help patients suffering from psychosis to overcome the obstacles left from trauma,⁵ and empirical validation with randomized controlled trials is needed in the future.

Our study has various limitations. First, while patient's follow-up was prospective, exposure to childhood trauma was assessed retrospectively in the current study, which may be particularly problematic for patients suffering from

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It is illegal to post this copy psychosis.⁴⁸ However, exposure to trauma was assessed over a rather intensive 3-year treatment on the basis of information obtained from patients and their families in the context of a trusting therapeutic relationship,⁴⁹ which may minimize the changes of recall bias existing in other forms of self-report or cross-sectional research interviews.⁵⁰ Second, although age at the time of first exposure to trauma and the repetitive nature of this exposure were recorded, there was no information about the duration of the period of maltreatment. We therefore were not able to verify previous findings that only childhood-onset abuse that persists through adolescence may have an impact on later outcomes.²⁷ Third, in our study, we focused on different kinds of traumatic experiences that have been associated with psychopathology in psychotic patients.¹³ Considering the limited size of the sample, we were not able to examine the differential effect of various types of childhood trauma on symptoms dimensions; it would be interesting to explore this issue in larger samples. Finally, other confounding factors (such as ethnicity, who

cheed PDF on any website. the perpetrator of the abuse was, or measures taken after the abusive episode) may have influenced the results, but these data were not available and therefore could not be taken into account.

In conclusion, our results suggest that the age at the time of occurrence of first trauma has a modulating effect on its impact on positive, depressive, and manic symptoms. In addition, they reveal that patients exposed to childhood trauma have more negative symptoms than do nonexposed patients, independent of the age at the time of exposure. These different impacts on symptom dimensions may have a neurobiological substrate, and further research is needed to explore the underlying mechanisms and ultimately develop new treatments. In parallel, considering that this subgroup of early psychosis patients deserves specific attention, more studies are needed to empirically validate the new psychological treatments that have recently been developed for severely traumatized patients suffering psychosis.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.



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Supplementary Material

- Article Title: Age at the Time of Exposure to Trauma Modulates the Psychopathological Profile in Patients With Early Psychosis
- Author(s): Luis Alameda, MSc; Philippe Golay, PhD; Philipp S. Baumann, MD; Carina Ferrari, MSc; Kim Q. Do, PhD; and Philippe Conus, MD
- **DOI Number:** 10.4088/JCP.15m09947

List of Supplementary Material for the article

1. <u>eTable 1</u> Demographic and Baseline Factors Related to Patients Included or Excluded From The Study

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary material.

	Total patients N = 240	Included in study N = 196	Excluded of study N = 44	Included vs Excluded (P-value)
Age in y, Mean (SD)	23.99(4.85)	24.06 (4.82)	23.68(4.99)	0.640
Sex, male, % (N)	69.2 (240)	70.9 (139)	61.4 (27)	0.278
SES, % (N) Low Inter. High	17.5 (42) 45.4 (109) 37.1 (89)	15.3 (30) 48.5 (95) 36.2 (71)	27.3 (12) 31.8 (14) 40.9 (18)	0.064
GAF Baseline, Mean (SD)	35.26 (15.52)	36.31 (15.42)	30.44 (15.26)	0.032
SOFAS Baseline, Mean (SD)	38.21 (15.88)	39.43 (15.81)	32.68 (15.17)	0.013
Diagnostic, % (N) Schizophren Schizophreniform/BPE. Schizoaffectif disorder Major depressionb Bipolar disorder Others	59.2(142) 11.3(27) 9.2 (22) 3.8(9) 6.7(16) 10.0(24	60,2 (118) 11.2 (22) 9.2 (18) 4.6 (9) 5.6 (11) 9.2(18)	54.5 (24) 11.4 (5) 9.1 (4) 0.0 (0) 11.4 (5) 13.6 (6)	0.456

Table 1. Demographic and baseline factors related to patients included or excluded from the study.

Note: Analyses between patients included or excluded of the study were performed with independent ttest for continuous variables and Fisher's exact test for categorical variables. BPE: Brief psychotic episode. ^a with psychotic features