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Childhood trauma, primary emotional systems, and suicidal ideation in youths with bipolar disorders

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Chapter 1

Suicide in youths with bipolar disorders

1.1 Juvenile bipolar disorders

It is currently accepted that bipolar spectrum disorders (BD) can be manifested in children and adolescents. A recent report by the International Society of Bipolar Disorders Task Force reported that the updated prevalence rate of BD is 2.06% (95% confidence interval 1.44%-2.95%), which appears to be relatively stable across studies (Goldstein et al., 2017). BD is more common than autism or schizophrenia and less common than depression or attention deficit hyperactivity disorder (ADHD) in pediatric age. Prevalence rates are higher in post-puberal samples than before puberty. Established risk factors for BD in youths are a family history of mood disorders, in particular BD, and, among environmental stressors, family conflict and high negative expressed emotion by family members (i.e., criticism, hostility, and emotional overinvolvement) (Goldstein et al., 2017). Recently, childhood traumatic experiences were also found to be specifically involved in juvenile BD (Cazala et al., 2019).

Diagnosis of juvenile BD requires changes in mood and behavior that are uncharacteristic of the individual and more extreme than developmentally appropriate, that persist long enough to meet duration criteria, and have a clear impact on functioning (American Psychiatric Association, 2013). Similarly to adult BD, juvenile BD displays extensive comorbidity (Merikangas et al., 2010). With the exception of developmental disorders, like ADHD and autism spectrum, the patterns of comorbidity are broadly consistent through youth and adult presentations. The presence of comorbid disorders worsens the course and outcome of juvenile BD. If comorbid disorders are present, mood symptoms need to be above and beyond the regular symptoms for the other disorders.

In terms of clinical presentation, irritability and emotional dysregulation are commonly present in youths with BD. Nevertheless, chronic irritability, regardless of severity, is not sufficient for a diagnosis of BD. Counting irritability as part of the diagnostic criteria for a manic/hypomanic episode requires that the irritability either begins or significantly increases in intensity in conjunction with the presence of accompanying manic symptoms (American Psychiatric Association, 2013).

Regarding the neurobiological underpinnings of juvenile BD, recent neuroimaging studies focused on the role of subcortical nuclei, in particular amygdala. Interestingly, meta-analytic findings reported that youths with BD present with smaller amygdala volumes than healthy controls (Pfeifer et al., 2008). These results are in line with meta-analytic findings in adults (D. P. Hibar et al., 2016). One prospective study that evaluated youth after their first manic episode, showed that amygdala volumes failed to show the expected normal increase with age in patients, whereas this did not occur in controls, suggesting that altered development of the amygdala may underlie the dysfunctional emotional processing reported in this type of patients (Bitter et al., 2011).

1.2 Suicide in juvenile general population

Overall suicide rates were recently estimated internationally by the World Health Organization to be 10.6/100,000 persons/year, accounting for 1.5% of all deaths (Fazel and Runeson, 2020). Annual suicide rates increased by 24% in the 15 years from 1999 to 2014. Increased rates were found for both sexes, ages 10–74 years, and in both rural and urban areas (Curtin et al., 2016; Rossen et al., 2018).

Suicide has been reported as the second leading cause of death among young persons aged 15–24 years worldwide (Fazel and Runeson, 2020). Suicide rates among adolescents in the international general population were recently estimated to be 3.77/100,000 persons/year, and to be higher among older adolescents, in particular males (Glenn et al.,

2020). Between 2010 and 2017, rates of suicide among adolescents/young adults aged 15–19 years increased in both sexes by 7.9% (Bould et al., 2019).

In Italy, the incidence of suicide amongst adolescents and young adults aged < 24 years amounts to 1.4/100 000 persons/year, and is 4.4 times more prevalent in males than in females (Castaldo et al., 2020). Suicide represents only a slim minority of instances of self-harm and suicide attempts, which may involve 5%–20% of all adolescents, although only 1 in 8 presents to clinical services, mostly for drug overdoses (Hawton et al., 2012).

1.3 Suicide in juvenile bipolar disorders

Suicide is the second leading cause of death worldwide among adolescents, and more than 80% of youths who have attempted suicide have received a diagnosis of a major affective disorder (Lewinsohn et al., 2002). Recent meta-analytic findings, including over 2,000 youths diagnosed with mood disorders, specified that the pooled incidence of suicide attempts in juvenile BD was 31.5% (De Crescenzo et al., 2017).

Reported risk factors for suicide attempts in juvenile BD patients include family history of suicide attempt, lifetime history of hospitalization, comorbid substance use disorder, panic disorder, non-suicidal self-injurious behavior, mixed episodes, psychotic features, and BD type I. Importantly, they also include history of physical and/or sexual abuse (Goldstein et al., 2005a). Furthermore, “mixed” manic-depressive features, including irritability, psychomotor agitation, and racing thoughts have strongly and consistently been associated with suicidal behaviors in adults, and there are indications of similar associations among youths with BD (Algorta et al., 2011).

Interestingly, a recent meta-analysis highlighted that the diagnosis of BD was associated with a higher rate of suicide attempts than the diagnosis of unipolar major depression, i.e., major depressive disorder (MDD) (De Crescenzo et al., 2017). The significance of the consistently higher risk of suicide attempts in juveniles and adults diagnosed with BD than

those with MDD may have different meanings. One possible explanation is that the combination of depressed or dysphoric mood with increased tendency to act, especially impulsively (as often found in BD, including mixed manic-depressive states), may result in the adoption of particularly lethal methods for committing suicide. In any case, these findings have important clinical implications concerning the early identification of BD, particularly in children and adolescents, as they encourage close monitoring of patients with juvenile mood disorders for potential suicidal risk. (De Crescenzo et al., 2017).

Chapter 2

Childhood trauma in bipolar disorders

2.1 Types of childhood traumatic events

Among environmental stressors, childhood trauma has emerged as one of the most important factors associated with bipolar disorders (BD). Childhood trauma could be conceptualized as either abuse or neglect. Childhood abuse includes any act or failure to act that resulted in actual or potential harm to a child. Neglect refers to the failure of a parent or any other person responsible for the child, to provide material necessities for the child's survival or to provide attention, love and support needed for the child's emotional development. Most of the studies in BD differentiated between childhood abuse (physical, sexual, or emotional) and neglect (emotional or physical) (Daruy-Filho et al., 2011). The Childhood trauma questionnaire (CTQ) has been the instrument most frequently used to assess early adverse events among these studies. The CTQ is a retrospective, self-report questionnaire assessing five different types of childhood trauma: Sexual abuse, physical abuse, emotional abuse, emotional neglect and physical neglect (Bernstein et al., 1994) (Table 2.1).

Table 2.1. Types of childhood trauma.

Abuse	Physical
	Sexual
	Emotional (Psychological)
Neglect	Physical
	Emotional (Psychological)

Childhood abuse and neglect have been reported by 51% of patients with BD. Specifically, 37% of patients with BD reported emotional abuse, 24% reported physical abuse, 24% emotional neglect, 21% sexual abuse, and 12% physical neglect. In addition, one-third of those patients presented a combination of different types of trauma (Daruy-Filho et al., 2011). A recent meta-analysis on 19 eligible studies demonstrated that childhood adversity was 2.63 times (95% CI 2.00–3.47) more likely to have occurred in patients with BD compared with healthy controls (HCs) (Palmier-Claus et al., 2016). Emotional abuse was four times more likely to have occurred in BD groups than in HCs, an effect seemingly larger than for other types of childhood adversity (OR=4.04, 95% CI 3.12–5.22). Palmier-Claus and colleagues (2016) did not find differences in rates of childhood adversity between BD type I (BD-I) and BD type II (BD-II).

Recently, we specifically addressed the question of whether the occurrence of childhood trauma was differently distributed in BD-I and BD-II. We found that all patients with BD had had more severe traumatic childhood experiences than HCs. Both BD-I and BD-II patients differed significantly from HC for emotional abuse. However, BD-I patients differed significantly from HCs for sexual abuse, and BD-II differed from HCs for emotional neglect (Janiri et al., 2014). Results indicated that the assessment of childhood trauma can unveil differences between BD subtypes and pointed out the importance of separately considering BD subtypes in the evaluation of childhood traumatic experiences.

2.2 Childhood trauma and clinical outcomes

Childhood trauma is a key determinant in the expression and clinical course of BD. There is a body of evidence relating the history of childhood maltreatment to a severe illness progression. In a review of 18 studies performed by Daruy-Filho and colleagues (Daruy-Filho et al., 2011), childhood abuse and neglect have been highlighted as specific risk factors associated with worse clinical outcome of BD. In a recent review, Aas and colleagues

(Aas et al., 2016) confirmed this observation. The association between childhood trauma and earlier age of onset appears to be consistent across studies. Both Daruy-Filho (Daruy-Filho et al., 2011), and Aas (Aas et al., 2016) underscored this result. The association is consistent across different types of childhood traumatic experience. The number of studies finding a link between earlier onset of BD and physical abuse (Leverich et al., 2002; Post et al., 2015) or emotional abuse/neglect (Etain et al., 2013; Li et al., 2014) appear to be nearly equal, whereas there is more evidence indicating sexual abuse as a risk factor to lower the risk for developing BD (Dienes et al., 2006; Etain et al., 2013; Leverich et al., 2002; Post et al., 2015). Childhood trauma also influences the recurrence of the illness. It has been associated with an increased number of mood episodes (Etain et al., 2013; Garno et al., 2005) and with a rapid cycling pattern. Patients tend to present a rapid-cycling pattern with an odds ratio (OR) of 1.96 if they reported physical abuse (Leverich et al., 2002) and with an OR of 2.04 if they reported sexual abuse (Etain et al., 2013). This increased risk appears particularly important in BD in regard to the unfavorable response to pharmacological treatment associated with rapid-cycling (Koukopoulos et al., 2003). Early adverse events have also been related to increased severity of mood symptoms. Garno and colleagues found increased manic⁄depressive symptom severity in patients who experienced childhood trauma (Garno et al., 2005). Nevertheless, authors did not discriminate the nature of childhood abuse in their analyses. Conversely, Leverich and colleagues specified that increased severity of mania was associated with childhood physical and sexual abuse (Leverich et al., 2002). Several authors also found that patients reporting childhood trauma presented with episodes marked by higher frequency of psychosis (Bebbington et al., 2011; Janssen et al., 2004; Romero et al., 2009). In an attempt to explain the relationship between psychosis and sexual abuse, some authors have suggested that affective symptoms, basically depression and anxiety, may primarily mediate this association (Bebbington et al., 2011). In agreement with this, a recent study found a specific significant association between

childhood abuse and auditory hallucinations, which was strongest for sexual abuse and hearing mood congruent voices (Upthegrove et al., 2015). The very strong association with suicidal behaviors can be considered the most important clinical outcome of childhood trauma in BD. Daruy-Filho et al. (Daruy-Filho et al., 2011) and Aas et al. (Aas et al., 2016) converged in showing the link between suicidality and early adverse events as a very stable result across studies in BD. Suicide attempts were specifically linked to emotional and sexual abuse (Etain et al., 2013; Janiri et al., 2018, 2014) and in particular to both emotional and sexual abuse in BD-I and only to emotional abuse in BD-II (Janiri et al., 2014). A recent study by our group identified, among several variables, emotional abuse as a direct predictor of suicide attempts in BD (Janiri et al., 2018). This study speculated that the high risk of suicide attempts found in patients reporting emotional abuse could be related to an inadequate emotional regulation. This in line with studies showing that emotional deregulation is linked to emotional abuse in BD (Aas et al., 2014a) and implicated in the neurobiology of suicide risk (Neacsiu et al., 2018). Our study (Janiri et al., 2018) specifically found an association between childhood emotional abuse and suicidal attempts, but not ideation. It is therefore, possible that childhood trauma can mediate the transition from ideation to action in patients with BD. Further longitudinal studies are needed to clarify this point.

2.3 Neuroimaging correlates of childhood trauma

Neuroimaging studies had a transformative influence on the field of neurobiological correlates of BD. They have firmly established BD as a brain disorder involving multiple, spatially distributed structural and functional brain abnormalities (Doucet et al., 2017; D P Hibar et al., 2016). In the last few years, neuroimaging studies have also provided evidence linking childhood traumatic experiences in BD to brain dysfunction (Table 2.2).

Structural volumetric changes have been found in patients with BD who experienced early adverse events. Duarte and colleagues (Duarte et al., 2016), using a voxel-based morphometry approach, found that BD-I patients showed a negative correlation between CTQ total score and gray matter volume in both the right dorsolateral prefrontal cortex (DLPFC) and the right thalamus. Specifically, they found that physical abuse and physical neglect were driving this association with the right DLPFC and the right thalamus, respectively. Bücker and colleagues (Bücker et al., 2014) found reduced volume of the corpus callosum in patients with BD with childhood trauma compared to BD patients without trauma. A study by our group found that amygdala and hippocampus volumes were differently affected by childhood trauma in patients with BD and HCs (Janiri et al., 2017). Specifically, childhood trauma was associated with bilaterally decreased volumes in HCs and increased volumes in patients with BD. This result emerged in the context of a global reduction of deep gray matter volumes in patients with BD. We speculated that increased amygdala volumes were related to an emotional overreactivity and increased hippocampal volumes to an over-representation of the traumatic experience. This observation is in line with the above-mentioned hypersensitivity to emotional stimuli and emotional dysregulation found in patients with BD.

Emotional dysregulation could also underline the results found in a recent study using functional magnetic resonance imaging (fMRI) during an emotion recognition paradigm in a sample of patients with BD or schizophrenia (Aas et al., 2017b). Authors found that higher levels of total childhood trauma were associated with a stronger differentiation in brain response to negative, compared to positive faces.

Some authors investigated in BD the influence of childhood trauma on structural brain connectivity. Stevelink and colleagues (Stevelink et al., 2018) found a global decrease in white matter integrity in patients with BD who experienced early adverse events compared to those who did not reported childhood trauma. Integrity of white matter microstructure was

assessed using DTI and quantified as fractional anisotropy (FA). Notably, childhood trauma could impact not only structural, but also functional brain connectivity in patients with BD. A resting-state fMRI (rs-fMRI) study found specific alterations in the limbic network (Souza-Queiroz et al., 2016) and a correlation between childhood trauma and decreased vmPFC-hippocampus (bilaterally) and prefronto-limbic functional connectivity (FC). These results confirmed the importance of the hippocampus as a potential key area in modulating early traumatic events in BD.

Table 2.2. Neuroimaging studies of the neurobiology of childhood trauma.

Study	Technique	Findings
Bücker et al., 2014	VBM	Reduced callosal volume in BD patients compared to HCs
Duarte et al., 2016	VBM	Total CTQ scores correlated inversely with gray matter volume in right DLPFC (correlation mainly driven by physical abuse) and in right thalamus (correlation mainly driven by physical neglect)
Souza-Queiroz et al., 2016	rs-fMRI	CTQ total scores were inversely correlated with amygdalar volume, with prefronto-limbic FC, and uncinate FA, results mainly driven by BD patients and entirely by physical and emotional neglect subscores
Janiri et al., 2017	VBM	Deep gray matter volumes globally reduced in BD patients, but childhood trauma related to decreased hippocampal and amygdalar gray matter volume in HCs and increased hippocampal and amygdalar gray matter volume in BD patients
Aas et al., 2017b	fMRI	In patients with BD or schizophrenia, stronger responses to negative than positive faces in an emotional face recognition task
Stevelink et al., 2018	DTI	BD patients with childhood abuse had lower FA in widespread brain regions compared to BD patients without childhood abuse; no differences between HCs with and without childhood abuse. Mean FA differences mediated the association between childhood abuse and BD, while childhood neglect showed no association with FA in both BD patients and HCs

Abbreviations: BD, bipolar disorder; CTQ, Childhood Trauma Questionnaire; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; FA, fractional anisotropy; FC, functional connectivity; fMRI, functional magnetic resonance imaging; HCs, healthy controls; rs, resting state; VBM, voxel-based morphometry

Chapter 3

Primary emotional systems

3.1 The Affective Neuroscience Theory

The term Affective Neuroscience (AN) was coined by Jaak Panksepp in 1992. His full theory (Montag et al., 2021; Panksepp, 1992) encompasses six primary emotional systems anchored in subcortical regions of the mammalian brain. With the recognition that it is highly probable that animals also have emotional feelings (Panksepp, 2006), Panksepp hypothesized that we should be able to shed light into core human emotional tendencies by studying animal brains. Accordingly, Panksepp carved out his emotional systems via deep brain stimulation, lesion studies and pharmacological challenges of the mammalian brain. All Panksepp's primary emotions represent evolved "tools for survival," which have been largely conserved across mammalian species, including humans. Since core emotional tendencies may emerge from ancient brain processes shared by all mammals, this approach also effectively allows one to utilize cross-species evolutionary strategies. Mammalian brains contain circuits that are critically involved in anger, fear, sexual lust, maternal care, separation distress, and social bonding, as well as playfulness and a general resource acquisition system for seeking/wanting — desires in a word (Panksepp, 2005). Each generates instinctual action tendencies that are easy to monitor in animal models. In his AN theory, Panksepp postulated that affective consciousness may have been built upon these inherited instinctual response tendencies (Panksepp, 2006). The hypothesis that core emotional feelings are firmly anchored in instinctual action systems of the brain, raises the interesting possibility that the foundations of consciousness are rooted in core affective processes (Panksepp, 2005).

3.2 Types of primary emotional systems

Panksepp divided the primary emotional systems in positive and negative emotional systems, briefly described as follows (for an overview, see Panksepp, 2006):

Positive emotional systems

PLAY: This is the system that allows to navigate social possibilities in joyous ways that can be easily monitored behaviorally. The urge to play was not left to chance by evolution, but is built into the instinctual action apparatus of the mammalian brain. This is an “experience expectant” system that bring young animals to the perimeter of their social knowledge. Such social activities help program brain circuits essential for well-modulated social abilities, perhaps partly by activating genes that promote neuronal growth and emotional homeostasis.

SEEKING: This dopamine-facilitated system energizes goal-directed urges and positive expectancies about the world. The SEEKING system generates a host of investigatory–exploratory activities. It is the one that mediates our intense appetitive motivation to obtain resources from the environment, and highlights how a basic state control system can readily link up with cognitive systems that mediate thoughtful awareness and appraisals.

CARE: The maternal instinct, so rich in all avian and mammal species, allows the human species to propagate effectively. This is the primary emotional system, still present in humans, that conditions the way we respond to newborn babies. It is based on changes of peripheral estrogen, progesterone, prolactin, and brain oxytocin occurring during a maternal state, through actions on extensive subcortical systems.

Negative emotional systems

FEAR: This is the system aroused by danger andprovokes freezing at lower arousal levels, and flight at higher levels. Although stimuli that intrinsically provoke fearfulness may differ among species, the evolved core structure of aroused FEAR is similar across all mammalian

species. The unconditional FEAR circuitry, that runs between the central amygdala to the periaqueductal gray of the midbrain, concurrently controls the instinctual action apparatus and those deeply aversive feelings that intrinsically help animals avoid danger. The evolutionary sense of this system relies on the fact that it is more adaptive to feel anticipatory fear than to be attacked and harmed.

ANGER: Anger can be evoked by a variety of situations. The RAGE system can be aroused by restraint, frustration and various other irritating stimuli, as well as directly by brain stimulation. Anger is provoked when organisms do not get what they want. Just like every subcortical emotional system, higher cortico-cognitive circuits are able to provide inhibition, guidance, and other forms of emotional regulation. Adults can modulate their anger in ways that children and animals cannot. The neuroscientific analysis of the ANGER circuitry has revealed neuropeptide controls, such as opioids and Substance P, which may eventually yield new pharmacological tools to facilitate such emotional self-regulation.

SADNESS: This system modulates intense separation distress. When children get lost, they cry out for care, and their feelings of sudden loneliness, verging on panic, may reflect the ancestral pain codes upon which adult sadness and grief are built. Brain systems yielding separation distress calls in mammals resemble each other so closely as to suggest a shared ancestral heritage. Brain chemistries that exacerbate feelings of distress (e.g., Corticotrophin Releasing Factor) and those that can powerfully alleviate distress (e.g., brain opioids, oxytocin, and prolactin) figure heavily in the genesis of social attachments.

3.3 Neurobiological underpinnings of primary emotional systems

According to Panksepp's studies, core emotional feelings arise rather directly from the neurodynamic of these basic emotional systems. The neurobiological underpinnings of primary emotional systems are shown in Table 3.1 (Panksepp, 2006).

Table 3.1. Neurobiological underpinnings of primary emotional systems		
Primary emotional systems	Key brain areas	Key neuromodulators
Positive emotional systems		
PLAY	Dorso-medial diencephalon, Parafascicular area, PAG	Opioids, Glutamate, ACh
SEEKING	Nucleus accumbens, VTA, Mesolimbic and mesocortical outputs, Lateral hypothalamus, PAG	Dopamine, Glutamate, Opiods, Neurotensin, Others
CARE	Preoptic area, VTA, PAG, Preoptic area, VTA	Oxytocin, prolactin, Dopamine, Opioids
FEAR	Amygdala, hypothalamus, PAG	Glutamate
ANGER	Medial amygdala	Substance P, ACh
SADNESS	Anterior cingulate, preoptic area	Opioids, Oxytocin, Prolactin, Glutamate

Abbreviations: ACh, acetylcholine; PAG, periaqueductal gray; VTA, Tsai's ventral tegmental area (A10). Norepinepherine and serotonin are not included since they modulate all emotional and cognitive processes. Adapted from Panksepp, 2006

Chapter 4

Childhood trauma, primary emotional systems and suicidal ideation in youths with bipolar disorders

4.1 Introduction

Bipolar disorders (BD) typically present with an age at onset that averages 15-25 years and a strong association with increased suicide risk. Recent meta-analytic findings, including over 2,000 youths diagnosed with mood disorder, specified that the pooled incidence of suicide attempts in juvenile BD was 31.5% (De Crescenzo et al., 2017). Suicidal ideation in adolescents predict the transition to future suicide attempts (Miranda et al., 2014). Previous findings showed that adolescents who reported suicidal ideation at age 15 had an almost 12 times higher risk of having attempted suicide by the age of 30, compared to adolescents who did not endorse suicidal ideation at baseline (Reinherz et al., 2006). Accordingly, the prompt identification of suicidal ideation in juvenile BD is crucial in fostering prevention and intervention planning.

While many studies have previously focused on clinical correlates of suicidal ideation in youths with BD (Hauser et al., 2013), emotional systems contributing to suicide risk in this population are poorly understood.

Jaak Panksepp, in his Affective Neuroscience Theory (Montag et al., 2021; Panksepp, 1992), proposed a theoretical framework to identify emotional endophenotypes, in which six primary emotional systems are closely related to specific subcortical neural system functions (Panksepp, 2006). SEEKING, CARE, and PLAY represent the positive primary emotional systems and relate, whereas ANGER, FEAR, and SADNESS can be found on the negative emotional side (capitalization is a convention used for labeling the emotional systems in Panksepp's frame). Interestingly, a recent study (Lu et al., 2021) assessing adults with BD during depressive episodes, found significantly higher negative and lower positive emotional

endophenotypes, as compared with healthy controls (HCs). However, the authors did not provide information about lifetime suicide risk.

Among early stressors, childhood trauma has emerged as one of the most important risk factors for BD (Daruy-Filho et al., 2011). Distinct types of traumatic experiences (i.e., sexual, physical, emotional abuse and neglect) differently impact on the course of illness in adult age and are associated with negative outcomes (Garno et al., 2005), specifically, increased suicide risk in both adults and youths (Cazala et al., 2019; Goldstein et al., 2005b; Janiri et al., 2018). Emotional abuse, in particular, has been indicated as the most important childhood trauma subtype in BD (Palmier-Claus et al., 2016) and was shown to specifically predict lifetime suicide risk (Janiri et al., 2018). Interestingly, a recent study demonstrated that a dysregulation in emotional systems mediated this relationship (Lemaigre and Taylor, 2019).

In the light of the above observations, we decided to test whether there is a specific relationship between suicidal ideation in youths with BD, primary emotional systems, and childhood trauma. We hypothesized that youths with BD and suicidal ideation would display higher negative and lower positive emotional endophenotypes and higher levels of childhood trauma, in particular emotional abuse, as compared with BD patients without suicidal ideation and HCs. To test this hypothesis, we assessed for the first-time individual differences in Panksepp's primary emotional systems and childhood traumatic events in a large sample of BD youths, with and without suicidal ideation, and age, sex-, and educational level-matched HCs.

4.2 Materials and methods

4.2.1. Participants

We consecutively assessed 103 young outpatients with a DSM-5 diagnosis of bipolar disorder (BD) type I, II, or unspecified. Patients were enrolled at the Early Intervention for Mood Disorders Unit at Fondazione Policlinico Universitario Agostino Gemelli IRCCS in

Rome, Italy. Patients were screened by trained staff for DSM-5 disorders, and clinical diagnoses were confirmed, using the Structured Clinical Interview for the DSM-5–Research Version (American Psychiatric Association., 2013). In addition to a diagnosis of BD, inclusion criteria were (i) age between 13 and 25 years (so to include teenagers and encompass all the usual BD onset range (Baldessarini et al., 2012); (ii) stable phase of illness according to psychometric evaluation (Hamilton Depression Rating Scale ≤ 7; Young Mania Rating Scale ≤ 12); (iii) fluency in Italian; and (iv) at least five years

of school education. Exclusion criteria were (i) traumatic head injury with loss of consciousness; (ii) lifetime history of major medical or neurological disorders; (iii) cognitive impairment; (iv) recent (past six weeks) changes in any psychotropic medication; (v) current use of stimulant medications; and (vi) a history of psychosis unrelated to the primary mood disorder. We also recruited 186 healthy controls (HCs), matched for age, sex, and educational level, from the same geographical area. All HCs were screened for current or lifetime history of DSM-5 disorders. For the aims of this study, we also interviewed them to determine their potential lifetime suicidal ideation; none of them reported lifetime suicidal ideation. HCs were also interviewed to assess whether any first-degree relative was affected by mood disorders or schizophrenia. If they had a positive family history, they were excluded. Other exclusion criteria for HCs were the same as those for the patient group. The study was approved and undertaken in accordance with the guidelines of the Fondazione Policlinico Universitario Agostino Gemelli Ethics Committee and in accordance with the Principles of Human Rights, as adopted by the World Medical Association (WMA) at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. All participants and their parents, if <18-years-old, gave their written informed consent to participate in the study after having received a complete explanation of the study procedures.

4.2.2. Clinical assessment

4.2.2.1 Suicidal ideation

The presence of a lifetime history of suicidal ideation was measured using the Columbia Suicide Scale for the Rating of Suicide Severity (C-SSRS) (Posner et al., 2011). Suicidal ideation was assessed according to the first section of the C-SSRS, an ordinal subscale composed by five items that address different components of the respondent's suicide ideation severity, such as the wish to be dead and active suicidal ideation with or without plan. Patients who reported any present of past suicidal ideation (i.e., any “yes” on the suicidal ideation subscale) were defined as BD-IS. Patients who did not meet these criteria were defined as BD-NIS. The C-SSRS has been validated in both adolescents and adults (Posner et al., 2011) and has demonstrated an excellent internal validity and an high degree of reliability. According to the FDA, it is considered the gold standard for the assessment of suicidal ideation and behavior in clinical trials (www.fda.gov).

4.2.2.2 Childhood trauma

We used the short form of the Childhood Trauma Questionnaire (CTQ) to measure early adverse childhood events. This is a 28-item, retrospective, self-report questionnaire (Bernstein et al., 2003) that investigates traumatic experiences in childhood; there are five possible answers, which range from “never true” to “very often true” depending on the frequency of the events. The questionnaire assesses five types of childhood trauma, i.e., emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. For each type of trauma, scores range from 5 to 25. Higher scores indicate greater childhood maltreatment. The CTQ has been used in youths in both nonclinical (Wang et al., 2022) and clinical populations (Cazala et al., 2019) with a high degree of reliability.

4.2.2.3. Affective Neuroscience Personality Scales

The Italian version (Pascazio et al., 2015) of the 2.4 Affective Neuroscience Personality Scales (ANPS), developed by Davis et al. (Davis and Panksepp, 2011) was used to assess Panksepp’s primary emotional systems. This scale is a 112-statement self-report inventory,

rated on a 4-point Likert scale (strongly disagree=0-strongly agree=3). It is designed to provide an assessment of all six basic affective systems that emerged from neuroscience research, i.e., SEEKING (interest), ANGER (rage), FEAR (anxiety), CARE (caring/nurturance), SADNESS (separation distress/grief), and PLAY (playfulness/joy). For a review of studies using the Affective Neuroscience Personality Scales in psychiatry, see Montag et al. (Montag et al., 2021).

4.2.3. Statistical analyses

We compared the socio-demographic and clinical characteristics of the three groups (i.e., BD-IS, BDI-NIS, and HCs) with the *chi*-square test for nominal variables and one-way analysis of variance (ANOVA) followed by post-hoc Scheffé tests for continuous variables and by pairwise post-hoc analyses for nominal variables. Significance was set at $p<0.05$.

For the first aim of this study, we focused on the distribution patterns of primary emotional systems and childhood trauma subtypes. First, we conducted a multivariate analysis of variance (MANOVA) using all the childhood trauma subtypes and the ANPS subscales as dependent variables, and the diagnostic groups (i.e., BD-IS, BD-NIS, and HCs) as independent factors. When the initial model was significant, we conducted a series of one-way ANOVAs, followed by Scheffé post- hoc tests, to compare means among groups. For comparative ANOVA measurements, we used a statistical model corrected for multiple comparisons according to the Bonferroni procedure ($P<0.05$/number of comparisons) to minimize the likelihood of type I statistical errors.

In addition, all the variables significantly different between the BD-IS and the BD-NIS group, along with sex and age, were subjected to a multivariate logistic regression model to generate Odds Ratios (ORs) and their 95% confidence intervals (CIs), with suicidal ideation as dependent outcome measures. We examined possible multicollinearity between variables of interest using variance inflation factor (VIF) indicator obtained from a linear regression analysis.

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (SPSS v. 25; IBM Corp., Armonk, New York, USA).

4.3 Results

4.3.1. Sociodemographic and clinical characteristics

The final sample included 289 individuals, 225 females (77.9%) and 64 males (22.1%), with a mean age of 18.95 (SD=3.64) years. In the entire sample of patients with a diagnosis of BD (n=103), 50 (48.5%) youths reported suicidal ideation during life time (BD-IS) and 53 did not (BD-NIS). The three diagnostic groups (i.e., BD-IS, BD-NIS and HCs) did not differ significantly for age, gender or educational level.

With respect to demographic characteristics, the three groups significantly differed for number of cohabitants and having divorced parents (Table 4.1). Specifically, post-hoc analyses clarified that HCs reported higher number of cohabitants than BD-NIS (p=0.01). BD-IS had higher rates of separated parents than BD-NIS (*Chi*-square=5.99, df=1, p=0.01) and HCs (*Chi*-square=22.61, df=1, p<0.0001) (Table 4.1).

With respect to clinical characteristics, BD-IS and BD-NIS significantly differed for family history, age at onset, hospitalization, use of antipsychotics, lithium and benzodiazepines (Table 4.1). BD-IS displayed higher rates of family history for psychiatric disorders and hospitalization and earlier age at onset then BD-NIS. They also reported more use of antipsychotics, lithium and benzodiazepine then BD-NIS (Table 4.1).

4.3.2. Distribution patterns of primary emotional systems and childhood trauma subtypes in patients with and without suicidal ideation

A preliminary MANOVA found a significant global effect (Wilk's Lambda=0.72, F=9.11, df=22, p<0.0001) of variables of interest on the presence of lifetime suicidal ideation (categorized as YES/ NO). Among primary emotional systems, factorial ANOVAs indicated a main effect of the SEEK, PLAY, CARE and ANGER systems, while the FEAR system did not survive to correction for multiple comparisons. Factorial ANOVAs indicated a main effect

for all types of childhood trauma, except for physical neglect, which did not survive to multiple comparison correction. In particular, with respect to emotional systems, a series of pairwise Scheffé *post hoc* analyses clarified that BD-IS scored higher on the ANGER system than both HCs and BD-NIS, while BD-NIS scored higher than HCs. Furthermore, BD-IS scored lower on the PLAY and the CARE systems than both HCs and BD-NIS, while BD-NIS scored lower than HCs. BD-IS and BD-NIS scored higher on the SEEK system than HCs (Table 4.2) (Figure 1).

BD-IS reported more emotional abuse, sexual abuse, physical abuse and emotional neglect than HCs, but only more emotional abuse than BD-NIS (Table 4.2) (Figure 2).

4.3.3 Primary emotional systems and childhood trauma on suicidal ideation

In the multivariate logistic regression, among variables associated with suicidal ideation, only the ANGER system and Emotional abuse significantly predicted suicidal ideation (Figure 3). The logistic regression model was statistically significant, $\chi^2(4) = 47.21$, $p<0.0001$. The model explained 61.0% (Nagelkerke R^2) of the variance and correctly classified 83.1% of cases. Specifically, increasing ANGER and childhood emotional abuse were associated with an increased likelihood to present with suicidal ideation (ANGER: OR=1.13, 95%CI=1.01-1.26, Wald=5.72; emotional abuse: OR=1.26, 95% C.I.=1.04-1.52, Wald=5.72).

4.4 Discussion

To our knowledge, this is the first study to date investigating Panksepp's primary emotional systems and childhood traumatic events in youths with BD with and without suicidal ideation. Consistent with our hypothesis, we found that youths with BD and suicidal ideation (DB-IS) displayed higher negative and lower positive emotional endophenotypes as compared to healthy controls (HCs) and patients without suicidal ideation (BD-NIS). In particular, BS-IS reported significantly higher scores on the ANGER system and lower scores on the PLAY

and the CARE systems than both HCs and BD-NIS, while BD-NIS reported higher and lower scores than HCs. With respect to childhood trauma, BD-IS reported more emotional abuse, sexual abuse, physical abuse and emotional neglect than HCs, but only more emotional abuse than BD-NIS. Notably, after modelling for all the significant variables, only ANGER and emotional abuse emerged as independent predictors of suicidal ideation in youths with BD (Figure 3).

The distribution pattern of primary emotional systems we found is in line with a previous study evaluating emotional endophenotypes in BD (Lu et al., 2021). Lu and colleagues assessed 43 adults with BD during a depressive episode and found that patients reported higher negative and lower positive emotional endophenotypes compared with HCs. Here, we extended this observation to juvenile BD and suicidal ideation. Our results are also in line with Panksepp's affective neuroscience theory, which postulates that emotional systems are commonly imbalanced in psychiatric disorders. This imbalance exists at the neuroanatomical, neurochemical, neurophysiology, and molecular genetics levels and may be important for making scientific sense of the emotional turmoil that commonly characterizes psychiatric syndromes (Panksepp, 2006). With respect to positive emotional systems, in our study we found decreased PLAY and CARE and increased SEEK in BD with suicidal ideation. According to Panksepp, the PLAY system is of primary importance for social bonding and possibly contributes to neocortical reward regulation (Panksepp, 2006). Children not allowed sufficient time to play may show difficulty in social contexts and in regulating experience-expectant learning (Greenough et al., 1987). According to this, aberrant social and reward processing were found to be implicated in juvenile BD (Nimarko et al., 2022; Schenkel et al., 2008; Schwarz et al., 2020) and suicidal ideation (Quevedo et al., 2022; Van Meter et al., n.d.). The CARE system elicits emotional urges to care for others (Montag et al., 2021). As a consequence, it has been hypothesized to be the main system involved in attachment alterations. Interestingly, attachment disturbances may characterize

patients with BD (Kefeli et al., 2018) and predict suicide risk (Grunebaum et al., 2010). Furthermore, a recent study found that patients with BD reported frequent abusive experiences in childhood along with higher levels of attachment insecurities (Kefeli et al., 2018). The SEEK system is implicated in goal directed activity and positive expectancies about the world. It is facilitated by dopamine circuits and mediates the primary process phenomenology of motivation (Panksepp, 2006). In our study we found increased SEEK in both BD-IS and BD-NIS compared to HCs, suggesting an effect of BD diagnosis on the SEEK system. Our results are in contrast with Lu and colleagues, who found reduced SEEK in patients with BD, as assessed through the ANPS (Lu et al., 2021). This discrepancy may be possibly explained by the clinical differences of the samples. Lu and colleagues evaluated adults during a depressive episode, whereas we assessed youths in a euthymic state. When novelty seeking is considered in adults as a temperament dimension, it was shown to constitute a heritable dimension (Jylhä et al., 2016) for BD and a risk factor for suicide (Greenwood et al., 2013). These findings are in line with our results, extending these observations to youths with BD.

Among primary emotional systems only ANGER significantly predicted suicidal ideation in youths with BD. According to Panksepp, the ANGER system can be aroused by restraint and frustration (Montag et al., 2021). It is challenged when individuals do not get what they want and it is sustained by amygdala activity (Reuter et al., 2009). Previous studies in adults found a specific association between anger and suicidal ideation or behaviors (Hawkins et al., 2014). In parallel, amygdala activity has been indicated as one of the neurobiological determinants of suicide risk (Kang et al., 2017). A very recent study found that individuals with past suicide attempt differed from those without attempts in their extended amygdala-hippocampal emotional reactivity to angry faces (Gilbert et al., 2022). The same study suggested that ketamine may revert this effect by regulating the circuits involved in emotional regulation (Gilbert et al., 2022).

Like every sub-neocortical emotional system, the ANGER system can be controlled by higher cortico-cognitive ones providing inhibition, guidance, and other types of emotional regulation (Panksepp, 2006). Accordingly, emotional regulation is implicated in the neurobiology of suicide risk (Neacsiu et al., 2018), being specifically increased in youths with suicidal ideation (Janiri et al., 2021).

In the present study we found an association between higher levels of childhood traumatic experiences, in particular emotional, sexual, physical abuse, and emotional neglect on one hand, and suicidal ideation on the other. Results are in line with previous evidence in literature (Kaplan et al., 1997; Stewart et al., 2015). Nevertheless, only emotional abuse emerged, along with ANGER, as an independent predictor of suicidal ideation in youths with BD. Our group has already shown a specific link between emotional abuse and suicide risk in adults with BD (Janiri et al., 2018, 2014). Here we extended these observations to a population of patients with BD with a large participation of teenagers. In a previous study we have also showed that childhood trauma could modulate amygdala gray matter volumes in BD (Janiri et al., 2017). As already mentioned, amygdala is also implicated in suicide risk and in modulating emotional response, in particular anger. Given that both ANGER and emotional abuse rely on the activity of the same amygdala circuits, we may speculate that early emotional traumatic experiences may alter amygdala activity and contribute to dysregulate emotional responses, including response to anger. In adolescence, these alterations might mediate an increased susceptibility to suicide risk in BD. Future longitudinal studies are needed to clarify these initial speculations.

According to our results, BD-IS had their onset at an earlier age and higher rates of family history, hospitalization, use of antipsychotic agents, lithium, and benzodiazepines then BD-NIS. These findings are in line with previous studies highlighting a more severe clinical outcome in adolescents reporting suicidal ideation (Reinherz et al., 2006). In this regard, our

study backs those authors who demand targeted interventions in key transition stages for youths presenting with suicide risk.

4.5 Limitations

Before presenting our conclusions, we must acknowledge some points that might limit the generalizability of our results. First, the cross-sectional design of our study limits the ability to investigate causal relationships between the assessed variables. Second, the reliability of the retrospective assessment of early traumatic experiences, as assessed with the CTQ, may be influenced by uncontrolled recall bias. Nevertheless, the CTQ is currently used in youths (Cazala et al., 2019; Wang et al., 2022) in both nonclinical (Wang et al., 2022) and clinical populations (Cazala et al., 2019) and is indicated as the best instrument for evaluating childhood trauma in BD (Daruy-Filho et al., 2011). Third, in our study girls were overrepresented compared to boys, accounting for over 70% of the total sample. Nevertheless, the three diagnostic groups (i.e., BD-IS, BD-NIS and HCs) were balanced for gender (p>0.05) and gender was considered in the multivariate model to exclude possible confounding effects.

Finally, despite the relatively large number of recruited patients, due to splitting of our samples into diagnostic groups, the final samples were relatively small.

4.6 Conclusions

Our study is the first to assess individual differences in Panksepp's primary emotional systems and childhood traumatic events in a sample of BD youths with and without suicidal ideation. We clarified that primary emotional systems and childhood traumatic experiences both contribute to suicidal ideation. In particular, the ANGER system and emotional abuse resulted to be independent predictors of suicidal ideation in juvenile BD. In clinical practice, all youths with BD who suffered childhood trauma, in particular emotional abuse, and presenting with high levels of anger, should be treated with particular attention because of their possible suicidal risk. The assessment of primary emotional systems and early trauma

would allow to better tailor prevention and enforce intervention strategies aimed at reducing suicide risk.

Table 4.1: Sociodemographic and clinical characteristics of BD-SI, BD-NSI and HC (N=289)						
Characteristics	BD-SI (n=50)	BD-NSI (n=53)	HC (n=186)	*F* or χ^2	df	*P*
Age (years): mean ± (SD)	17.82 (3.71)	19.34 (4.07)	19.15 (3.46)	3.006	2	0.051
Gender, males: n (%)	8 (16.0)	13 (24.5)	43 (23.1)	1.372	2	0.504
Educational level (years): mean ± (SD)	12.20 (3.03)	13.20 (3.09)	13.37 (2.87)	2.874	2	0.058
Number of cohabitants: mean ± (SD)	3.80 (0.90)	3.57 (0.77)	3.98 (0.90)	4.905	2	0.008
Separated parents: n (%)	29 (58.0)	18 (34.0)	43 (23.1)	22.601	2	<0.001
Family history of psychiatric disorders: n (%)	32 (64.0)	23 (43.4)	-	4.389	1	0.036
Age at onset (years): mean ± (SD)	14.02 (2.48)	15.67 (4.40)	-	4.366	1	0.040
Hospitalizations: n (%)	15 (30.0)	7 (13.2)	-	4.319	1	0.038
Treatment adherence						
Completed adherence: n (%)	42 (84.0)	44 (83.0)	-	0.49	2	0.78
Partial adherence: n (%)	5 (41.7)	7 (58.3)	-			
Partial adherence: n (%)	3 (6.0)	2 (3.8)	-			
Treatments						
Antidepressants: n (%)	13 (26.0)	12 (22.6)	-	0.158	1	0.691
Antiepileptics: n (%)	21 (42.0)	17 (32.1)	-	1.088	1	0.297
Antipsychotics: n (%)	17 (34.0)	8 (15.1)	-	5.003	1	0.025
Lithium: n (%)	13 (26.0)	1 (1.9)	-	12.737	1	<0.001
Benzodiazepines: n (%)	12 (24.0)	5 (9.4)	-	3.961	1	0.047
Psychotherapy: n (%)	25 (50.0)	19 (35.8)	-	2.105	1	0.147
BD-SI= bipolar disorder-Suicidal-Ideation; BD-NSI=Bipolar Disorder-Non Suicidal Ideation; HC=Healthy Controls; SD=Standard deviation; df=Degrees of freedom.						

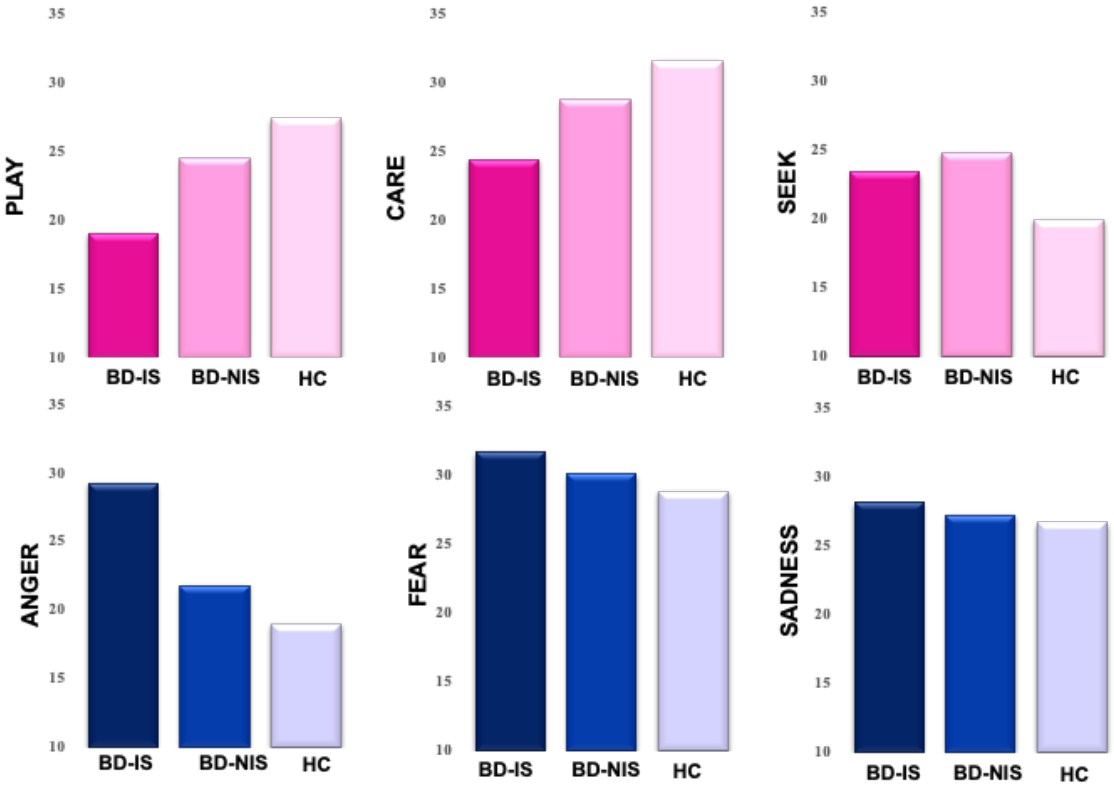
Table 4.2: Distribution patterns of childhood trauma subtypes and primary emotional systems in BD-SI, BD-NSI and HC (N=289)

	SI mean ± (SD)	NSI mean ± (SD)	HC mean ± (SD)	*F* or χ^2	df	*P*	HC vs BD-SI (*P*)#	HC vs BD-NSI (*P*)#	BD-SI vs BD-NSI(*P*)#
Primary emotional systems according to the ANPS									
SEEK	23.43 (7.49)	24.78 (6.10)	19.90 (6.18)	14.180	2	<0.001*	0.004	<0.001	0.590
PLAY	19.11 (6.93)	24.44 (7.49)	27.38 (6.07)	30.394	2	<0.001*	<0.001	0.02	<0.001
CARE	24.41 (8.75)	28.70 (5.81)	31.60 (5.90)	23.713	2	<0.001*	<0.001	0.020	0.006
FEAR	31.67 (6.49)	30.13 (5.49)	28.89 (6.31)	3.921	2	0.021	0.026	0.464	0.472
ANGER	29.26 (7.43)	21.80 (6.47)	19.01 (6.02)	47.821	2	<0.001*	<0.001	0.024	<0.001
SADNESS	28.07 (6.70)	27.24 (5.03)	26.69 (6.40)	0.927	2	0.397	0.412	0.859	0.810
Childhood trauma subtypes according to the CTQ									
Emotional abuse	14.50 (5.52)	10.38 (4.06)	8.19 (3.60)	44.508	2	<0.001*	<0.001	0.004	<0.001
Physical abuse	7.22 (3.44)	6.42 (2.43)	5.69 (2.31)	7.134	2	0.001*	0.002	0.201	0.312
Sexual abuse	6.87 (3.16)	6.08 (2.32)	5.41 (2.25)	7.016	2	0.001*	0.002	0.321	0.287
Emotional neglect	13.74 (3.38)	12.58 (2.47)	12.0 (2.42)	8.233	2	<0.001*	<0.001	0.384	0.097
Physical neglect	10.20 (1.80)	9.86 (1.83)	9.42 (1.48)	4.953	2	0.008	0.014	0.226	0.593

BD-SI= Bipolar Disorder-Suicidal-Ideation; BD-NSI=Bipolar Disorder-Non Suicidal Ideation; HC=Healthy Controls; SD=Standard deviation; df=Degrees of freedom; * P significant after Bonferroni correction; Scheffé *post hoc* tests

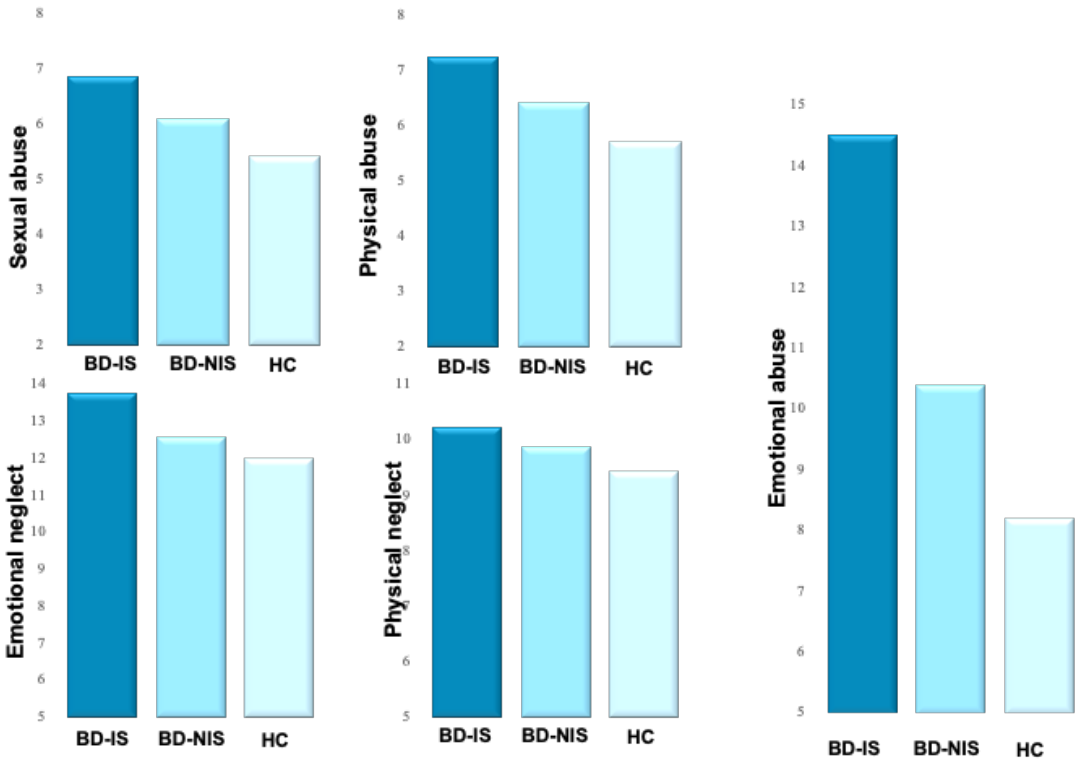
ANPS, Affective Neuroscience Personality Scale; CTQ, Childhood trauma questionnaire

Figure 1: Distribution patterns of primary emotional systems according to the ANPS in BD-SI, BD-NSI and HC (N=289)



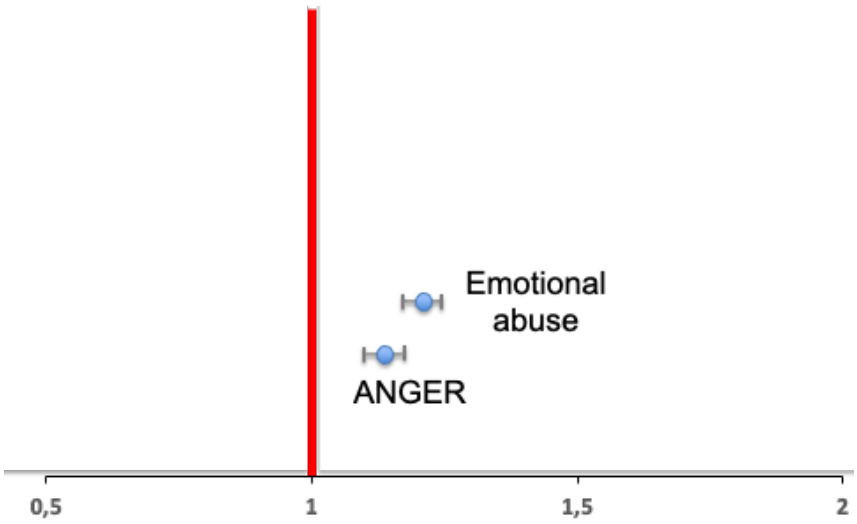
Legend: BD-SI= bipolar disorder-Suicidal-Ideation; BD-NSI=Bipolar Disorder-Non Suicidal Ideation; HC=Healthy Controls; ANPS, Affective Neuroscience Personality Scale. Mean of all ANPS subscales are provided.

Figure 2: Distribution patterns of childhood traumatic experiences according to the CTQ in BD-SI, BD-NSI and HC (N=289)



Legend: BD-SI= bipolar disorder-Suicidal-Ideation; BD-NSI=bipolar disorder-Non-Suicidal Ideation; HC=Healthy Controls; CTQ, Childhood trauma questionnaire. Mean of all CTQ subscales are provided.

Figure 3: Prediction of risk of suicidal ideation



Odds Ratios (ORs) and their 95% confidence intervals (CIs) are reported for risk factor predicting suicidal ideation

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