Hippocampal subfield volumes and childhood trauma in bipolar disorders

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Abstract

Background: Childhood trauma is associated with risk for bipolar disorders (BD). Alterations in hippocampal structure and function are present in BD. The hippocampus consists in subfields with distinct morphology that are differently sensitive to stress. The current study aims to test the hypothesis that childhood trauma may be differentially associated with hippocampal subfield volumes in BD and HC.

Methods: One hundred and four patients with BD type I (BDI) and BD type II (BDII) and 81 healthy comparison (HC) individuals underwent high-resolution structural magnetic resonance neuroimaging. The volumes of all hippocampal subfields were measured using FreeSurfer. The history of childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ).

Results: Patients with BD presented lower volumes of hippocampal subfields compared to HCs. Childhood trauma was associated with lower volumes in HCs and higher volumes in patients with BD selectively on bilateral subiculum, presubiculum and CA1. This effect was more prominent in BDII than in BDI.

Limitations: Recall bias may influence the reliability of the retrospective assessment of childhood trauma experiences.

Conclusions: Childhood trauma is differently associated with hippocampal subfield volumes in patients with BD and HCs. Specifically, hippocampal subfields implicated are those primarily involved in emotion regulation.

Keywords: Bipolar disorders, Hippocampus, Childhood trauma, Neuroimaging, Hippocampal subfields

Highlights:

- Smaller hippocampal subfields in patients with bipolar disorders than controls.
- Childhood trauma in controls is associated with smaller hippocampal subfields.
- Childhood trauma in bipolar disorder is associated with larger hippocampal subfields.
- Childhood trauma affected mostly Subiculum, Presubiculum and Cornu Ammonis 1

1. INTRODUCTION

Childhood trauma is an environmental stressor associated with risk for both type I and type II bipolar disorders (BD) (Daruy‐Filho et al., 2011; Janiri et al., 2014; Palmier-Claus et al., 2014). The hippocampus is critically implicated in the biological response to stress (Herman and Mueller, 2006; Panaccione et al., 2017; Pruessner et al., 2017) as it is involved in the processing of traumatic memories (Small et al., 2001) and in the emotional response to trauma (Chalavi et al., 2015; Teicher et al., 2012; Wang et al., 2010). A recent meta-analysis (Calem et al., 2017) revealed that hippocampal volumes are affected by childhood adversity in general population samples, with greater levels of such adversely associated with lower hippocampal volumes, reinforcing similar associations between childhood stress and hippocampal volumes in clinical samples of persons with depression (Opel et al., 2014) or post-traumatic stress disorder (Ahmed-Leitao et al., 2016).

Consistent with the neurobiological functions supported by the hippocampus as well as its susceptibility to the effects of psychosocial stress, relatively lower hippocampal volumes are consistently correlated with BD, regardless of subtype. The largest study to-date, which compared 1710 patients with BD to 2594 healthy comparison (HC) individuals, found that, amongst the limbic and diencephalic structures evaluated, lower total hippocampal volume was the finding with the largest effect size (Hibar et al., 2016). BD-related effects on hippocampal volumes have been reported for all hippocampal subfields (Elvsåshagen et al., 2013; Haukvik et al., 2015a; Janiri et al., 2018; Mathew et al., 2014), with the most pronounced effects on the cornu ammonis (CA) (Haukvik et al., 2015b; Mathew et al., 2014). However, the relationship between childhood adversity and hippocampal volume in BD is both limited and inconsistent. There is evidence (Souza-Queiroz et al., 2016) of lack of association between childhood trauma and hippocampal volume in a relatively small study

that included 32 persons with BD. On the contrary, Aas and colleagues (Aas et al., 2014b) observed an association between hippocampal volumes and childhood adversity in BD only among *met* carriers of the *val66met* allele of the BDNF gene. We investigated the effect of childhood trauma on deep grey matter structures in BD and found that it was associated with bilateral increase of the total hippocampal and amygdala volumes in patients with BD and the opposite in HCs (Janiri et al., 2017). Nevertheless, in our previous study we have not specifically considered how childhood trauma impacts on the anatomical complexity of hippocampus. Indeed, the hippocampus consists of subfields with distinct morphology (i.e. the cornu ammonis (CA) subfileds CA1-4, the dentate gyrus (DG), fimbria, subiculum and presubiculum), which could be differently sensitive to early-life stress in BD.

In the present study, we test the patterns of association between childhood trauma and the volumes of the hippocampal subfields.

2. MATERIAL AND METHODS

The study was approved by the Santa Lucia Foundation Ethics Committee and was undertaken in accordance with the Principles of Human Rights, as adopted by the World Medical Association 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 gave their written informed consent to participate in the study after they had received a complete explanation of the procedures.

2.1 Participants

Consecutive outpatients with DSM-IV-TR (American Psychiatric Association, 2000) diagnoses of BD were identified at the Sant'Andrea clinic in Rome and the outpatient clinic of the IRCCS Santa Lucia Foundation in Rome, Italy. They were subsequently evaluated using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P) (First

et al., 2002a). Diagnostic interviews were conducted by raters with extensive training and demonstrably high interrater reliability (k >0.8).

In addition to a SCID-I/P diagnosis of BD, inclusion criteria were: (i) age 18-75 years; (ii) at least five years of education; (iii) able to undergo magnetic resonance imaging (MRI); (iv) Italian language native speaker; (v) at least six months of stable pharmacotherapy for BD; and other non-exclusory conditions. Exclusion criteria were: (i) diagnosis of substance dependence or abuse in the two years before the assessment; (ii) traumatic brain injury with loss of consciousness; (iii) major medical or neurological disorders; (iv) Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score lower than 24 (given that scores below this level are suggestive of cognitive difficulties based on normative data from the Italian population) (Measso et al., 1993); (v) left-handedness; and (vi) any MRI-idenitified brain abnormality or microvascular lesion on T1-weighted, T2-weighted images, or fluid attenuated inversion recovery (FLAIR) sequences; (vi) incomplete or incorrect scan segmentation.

HCs were recruited from the same geographical area. All HCs were screened for lifetime personal history of DSM-IV-TR Axis I and II disorders using the SCID-I/NP (First et al., 2002b) and SCID-II (First et al., 1997) as well as for family history (up to 2nd degree relatives) of mood disorders or schizophrenia. Participants with DSM-IV-TR Axis I or II disorders and/or family history of mood disorders or schizophrenia were excluded from the HC group. All other eligibility criteria were the same as those for the BD group.

In total, 123 patients and 113 HCs were referred over a period of 1 year. One hundred and four patients and 81 HCs were included in the present study according to inclusion/exclusion criteria.

The sample overlap between present study and our previous study on childhood trauma and deep grey matter structures (Janiri et al., 2017) in BD was 85%. Specifically, one patient and

32 HCs were excluded because of errors in the segmentation of the hippocampus into its respective subfields.

2.2 Clinical assessment

Age at onset was defined as the age at onset of the first clinically significant mood episode of any polarity. The severity of psychopathology on the day of the scan was assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978), the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) and the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959).

Childhood trauma was assessed by the short form of the Childhood Trauma Questionnaire (CTQ), a 28-item, retrospective, self-report questionnaire that evaluates traumatic experiences in childhood (Bernstein et al., 2003). The CTQ has been used in both non-clinical (Teicher et al., 2012; Walker and Unutzer, 1999) and clinical populations (Kilian et al., 2017; Monteleone et al., 2018) and in neuroimaging studies. It has a high degree of reliability and it was also recently used to assess patients with BD. The questionnaire examines five different types of trauma: emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse. Responses to trauma-focused questions are rated on a five-point scale ranging from “never true=1” to “very often true=5.” The scale yields a summary score (range from 25 to 125) as well as a score for each trauma subtype (range from 5 to 25). Higher scores indicate higher levels of childhood trauma and cut off scores for each type of trauma are used to yield four levels of maltreatment: none, low, moderate and severe(Bernstein et al., 1994). If 1 or more subscales met the cut-off criteria for moderate or severe trauma, participants are considered to have a history of that childhood trauma subtype (Bernstein and Fink, 1998; Walker and Unutzer, 1999).

2.3 MRI protocol

Participants underwent an imaging protocol which included 3D T1-weighted, T2-weighted and FLAIR sequences, using a 3T Achieva MR imager (Philips, Amsterdam, The Netherlands) with a standard quadrature head coil. Whole-brain T1-weighted images were obtained in the sagittal plane using a MPRAGE sequence (TE/TR = 5.4/11 ms, flip angle 8°, voxel size 0.54×0.54×0.9 mm3). Only T1-weighted images were used in the analysis.

T1 weighted images were processed using FreeSurfer 5.3 image analysis pipeline (Martinos Center for Biomedical Imaging, Boston, Massachusetts), in particular the *aseg* algorithm. In brief, the processing relevant to this work includes removal of non-brain tissue by using a hybrid watershed/surface deformation procedure (Segonne et al., 2004) automated Talairach transformation and segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2004, 2002). In subjects with substantial anatomical differences with respect to the template, e.g., enlarged ventricles, the resulting segmentation of the subcortical structures was improved by a pair-wise registration of their images to training images (Sabuncu et al., 2010). Next, segmentation of the hippocampus into its respective subfields was performed by using Bayesian inference and a previously described statistical model of the medial temporal lobe (Van Leemput et al., 2009). The Dice overlap measures between manual and automated segmentation methods were approximately 0.7 for all of the substructures (Van Leemput et al., 2009). We focused on the volume of the CA1, CA2/3, CA4/dentate gyrus, presubiculum and subiculum and excluded from the analyses the fimbria (which is a white matter region), hippocampal fissure and the final portion of the hippocampal tail, which is not sub-dividable in any of the subfields. All the volumes were corrected for Intracranial Volume (ICV) according to the proportion method (Sanfilipo et al., 2004).

2.3 Statistical analyses

2.3.1 Main analyses

2.3.1.1. Demographic and clinical characteristics

Sociodemographic and clinical characteristics of the diagnostic groups (i.e. BDI-CT, BDI-nCT, BDII-CT, BDII-nCT HC-CT and HC-nCT) were compared using the chi-square test for nominal variables and one-way analysis of variance (ANOVA) for continuous variables. The alpha level for these tests was set at $p = 0.05$.

2.3.1.2 *Hippocampal subfields*

A series of multivariate analyses of variance (MANOVA) were conducted for each hemisphere using all the ICV-corrected volumes of the hippocampal subfields as the dependent variables; diagnosis (BDI, BDII and HC) and the presence of childhood trauma (CT+, CT-) as independent factors; and sex (M, F) to verify the impact of this variable on the main analyses. When the initial model was significant, a series of two-way analyses of variance (ANOVAs) on hippocampal subfield volumes setting diagnosis and childhood trauma as independent variables then were performed. When a significant main effect of the diagnosis and the interaction between the diagnosis and childhood trauma was identified, student t-tests to assess for between-group differences in hippocampal subfield volumes then were performed. 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 (false positive) statistical errors.

2.3.2 Follow-up supplemental analyses.

We repeated the ANOVAs on all the hippocampal subfield volumes using lithium, antidepressants and antipsychotics status as independent factor, together with CT+ CT-, to evaluate the role of medication on results. Moreover, we conducted ANCOVAs on all the hippocampal subfield volumes, setting diagnosis and CT+ CT- as independent factors and duration of illness as covariate, to further rule out its possible confounding effect.

3. RESULTS

3.1 Demographic and clinical characteristics

The characteristics of the sample are shown in Table 1.

3.2 Hippocampal subfields

In the left hemisphere, the MANOVA revealed a significant effect of diagnosis on all ICV-corrected hippocampal subfield volumes (Wilks' Lambda=0.72; F=5.83; df =10; P<0.0001), a significant effect of sex (Wilks' Lambda=0.91; F=3.29; df =5; P=0.007), and a significant interaction between diagnosis and childhood trauma (Wilks' Lambda=0.88; F=2.18; df =10; P=0.01).

In the right hemisphere, the MANOVA revealed a significant effect of diagnosis on all ICV-corrected hippocampal subfield volumes (Wilks' Lambda=0.78; F=4.25; df =10; P<0.0001), a significant effect of sex (Wilks' Lambda=0.92; F=2.59; df =5; P=0.02), and a significant interaction between diagnosis and childhood trauma (Wilks' Lambda=0.89; F=1.94; df =10; P=0.03). There was no interaction between sex, diagnosis and childhood trauma on hippocampal subfields in either hemisphere.

The ANOVAs revealed significant bilateral effects of diagnosis on all hippocampal subfields. Moreover, a significant effect of childhood trauma on bilateral presubiculum and a significant effect of the interaction between diagnosis and childhood trauma on bilateral CA1, presubiculum and subiculum were observed (see Table 2 and Figure 1).

Pairwise t-test did not identify differences in hippocampal subfield volumes between the two patient subgroups (BDI and BDII) but hippocampal subfield volumes in both groups were smaller than those observed in the HCs (see Table 3). Pairwise between-group t-tests are presented in Table 4.

3.3 *Follow-up supplemental analyses*

ANOVAs revealed no significant interactions between childhood trauma and medications on hippocampal subfield volumes in either hemisphere. ANCOVA also failed to reveal significant

interactions between diagnosis, childhood trauma and duration of illness on hippocampal subfield volumes in either hemisphere.

4. DISCUSSION

Childhood trauma is associated with bilaterally smaller CA1, presubiculum and subiculum volumes among HCs whereas childhood trauma was associated with comparatively larger CA1, presubiculum and subiculum volumes among persons with BD. The present findings are consistent with those that our research group reported previously, i.e., that childhood trauma was associated with lower total hippocampal volumes in HCs (Janiri et al., 2017).

Although the association between childhood adversity and lower total hippocampal volume in HCs is fairly consistent (Calem et al., 2017), this association does not appear to hold as consistently for the CA1, presubiculum and subiculum subfields. Teicher and colleagues (Teicher et al., 2012) reported that childhood adversity was associated with lower volumes in all left-sided hippocampal subfields, with the effect being more prominent in the CA2-CA3 and CA4/dentate gyrus in young HCs. The present findings are complementary to those of Teicher and colleagues, albeit with a focus CA1 and subiculum/presubiculum.

Among hippocampal subfields, the CA1 and subiculum/presubiculum are the principal points of outflow of the hippocampal neuronal circuitry (van Strien et al., 2009) and have reciprocal connections to the amygdala, the medial prefrontal and orbitofrontal cortices, the nucleus accumbens and the anterior and posterior cingulate cortex (Rosene and Van Hoesen, 1977). Thus, CA1 and subiculum/presubiculum are implicated not only in memory but also in emotion regulation and are plausible targets for stress-related reactivity (O'Mara et al., 2009). The mechanisms mediating the association between childhood trauma and these hippocampal subfield volumes in HCs have not been fully delineated. However, current models suggest that stress-related overactivation of the hippocampus and hippocampus

circuits connected with the amygdala (Tottenham, 2009) and N-methyl-D-aspartate (NMDA) receptor mediated toxicity associated with elevated levels of glucocorticoids (Armanini et al., 1990) may damage the hippocampus and result in smaller hippocampal volumes.

The larger volumes of CA1, subiculum/presubiculum observed in persons with BD and childhood trauma require other explanatory neurbiological mechanisms. One possibility is a specific BD-associated resistance to stress that may protect against neurotoxic effects on the hippocampus, although the neurobiological foundation for a resistance of this type has not been established. Although still entirely speculative, it is possible that there is a BD-associated decoupling, or aberrant coupling, of trauma-related emotional responses in BD that alters the effects of trauma on hippocampal subfield volumes. To point, Minkoswski (Minkoswski, 1927) reported an emotional deregulation in patients with BD – specifically, an excessive emotional "synchronism" with life experience that has been recently conceptualised as a hyper-reactivity to emotional stimuli (Corbalán et al., 2015; M'bailara et al., 2009). Similarly, affective lability also is associated with childhood trauma among persons with BD (Aas et al., 2017, 2014a). It is possible that the combination of persistent BD-associated and childhood trauma-exacerbated emotional hyper-reactivity in BD may engender alterations in the structure and function of limbic and paralimbic structures involved in the generation, expression, and regulation of emotion, including the abnormal hippocampal subfield volumes observed in the present study. We therefore hypothesize that comparatively larger subiculum volumes observed among persons with BD and childhood trauma in the present study are the product of emotional hyper-reactivity-related activation of the extended amygdala, ventral-striato-pallidum, and brainstem limbic stuctures - particularly the ventral tegmental area (VTA), the regulation of which is contributed to substantively by the hippocampus (Cooper et al., 2006; O'Mara et al., 2009).

The VTA, the principal source of projections in the dopaminergic mesolimbic pathway, is an

essential component of reward and emotion processing. VTA dopaminergic neurons fire in response to emotional stimuli, and the magnitude of their response varies with the magnitude of the emotional response; as such, hypersensitivity to emotional stimuli among persons with BD and childhood trauma (Aas et al., 2014a) reflects greater activation of the VTA and the limbic and paralimbic structures to which it projects. VTA activity, in turn, is further modified by two systems: the brainstem pedunculopontine tegmentum (PPTg) and the hippocampus – and, more specifically, the subiculum (Grace, 2012).

The PPTg elicits the phasic burst firing in response to environmental salient stimuli and the subiculum controls the number of DA neurons firing when the burst occurs (Grace, 2012). Hippocampal regulation of VTA dopaminergic neurons is effected by presubiculum/subiculum (predominantly CA1) projections to the nucleus accumbens which, in turn, projects to the ventral tegmental area (VTA) via ventral pallidum (Cooper et al., 2006). Accordingly, subiculum modifies VTA activity in a manner that provides amplified responses to emtional stimuli. Persistent amplified activation of the subiculum among persons with BD and childhood trauma may thereby contribute to the comparatively larger subiculum and related hippocampal subfield volumes observed among these participants in the present study.

The CA1, presubiculum, and subiculum are also involved in memory processes (O'Mara et al., 2009). Specifically, CA1 and subicular neurons participate, with different delays in response to the stimuli, to the construction of episodic memory (Deadwyler and Hampson, 2006). The CA1, presubiculum, and subiculum are connected with the amygdala directly and via the enthorinal cortex (Lavenex and Amaral, 2000; Rosene and Van Hoesen, 1977) and are specifically involved in the modification of memory for context-specific fear and its extinction (Ji and Maren, 2007), including responses to stress and fear. While stress-related changes in hippocampal volume in HCs has been associated with disruptions in memory (Gianaros et al.,

2007), the comparatively larger CA1, presubiculum, and subiculum volumes among persons with BD and childhood trauma in the present study may reflect, as contributor and/or consequence, engagement of these structures in the development and emotional stimuli-related elaboration of traumatic memories (O'Mara et al., 2009). Interestingly, we found elevated anxiety scores in patients with BD and concomitant childhood trauma and in our previous study we found similar associations with amygdala volumes (Janiri et al., 2017) in this population.

While these interpretations of the present study findings must be regarded as speculative, they are hypothesis-generating and inform next steps in this line of scientific inquiry. Replication of these and prior related findings and extension of this work into longitudinal studies are needed to clarify the nature of association between CA1, presubiculum, and subiculum volumes among persons with BD and childhood trauma and the functional relevance of the comparatively larger volumes of these structures in this population.

Limitations:

Several limitations of the present study require consideration both in relation to interpretation of the observations made herein as well as in consideration of the design of future studies. First, while the CTQ is among the best instruments for assessing childhood trauma in BD patients (Daruy‐Filho et al., 2011), recall bias may influence the reliability of the retrospective assessment of childhood trauma experiences. Second, the present study was not adequately powered to evaluate associations between the five subtypes of childhood trauma in BD assessed by this instrument (i.e., emotional abuse, sexual abuse, physical abuse, emotional neglect, physical neglect) and the hippocampal subvolumes upon which this work focused. Third, the present study did not identify an effect of lithium treatment on hippocampal subfield volumes; this observations stands in contrast with previously observed short- and long-term effects of lithium on hippocampal volumes among persons with BD

(Hajek et al., 2014; Sani et al., 2018; Simonetti et al., 2016). While retrospective (including chart-based) determinations of the duration and magnitude (i.e., dosing) of lithium exposure were common to this and other studies, this method may not yield data of sufficiently high fidelity and reliability to adequately evaluate the effects of lithium on hippocampal sub-volumes.

Several strengths of the present methods also merit consideration in relation to interpretation of findings from this study and the design of future ones. Perhaps the most noteworthy of these is the separate consideration of persons with BD type I and type II. Several prior investigations like ours did not consider the clinical distinctions between these BD subtypes and instead aggregated persons with them into a single group for the purpose of neuroimaging analyses. The present study reveals that childhood trauma contributes to differences between BD subtypes (Janiri et al., 2017, 2014) and emphasizes the importance of considering separately BD subtypes in neuroimaging studies in which the effects of childhood trauma are a focus of the investigation.

In conclusion, our results highlight the differential effects of childhood trauma on hippocampal subfields among persons with BD and HCs Among persons with BD and childhood trauma, comparatively larger CA1, presubiculum and subiculum volumes were observed. Interestingly, CA1 and subiculum/presubiculum have been indicated as potentially important anatomic mediators of response to antipsychotic and lithium (Greene, 1996) and a relatively recent study described that childhood trauma is associated with a poor response to lithium among persons with BD (Etain et al., 2016). In light of our findings, it could be very important to elucidating the effect of childhood trauma on these structures among patients with BD because it may permit to refine the treatment approach to BD with and without concomitant childhood trauma.

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Figure 1 title:

Volumes of the hippocampal subfields in patients with bipolar disorders and in healthy individuals with or without childhood trauma.

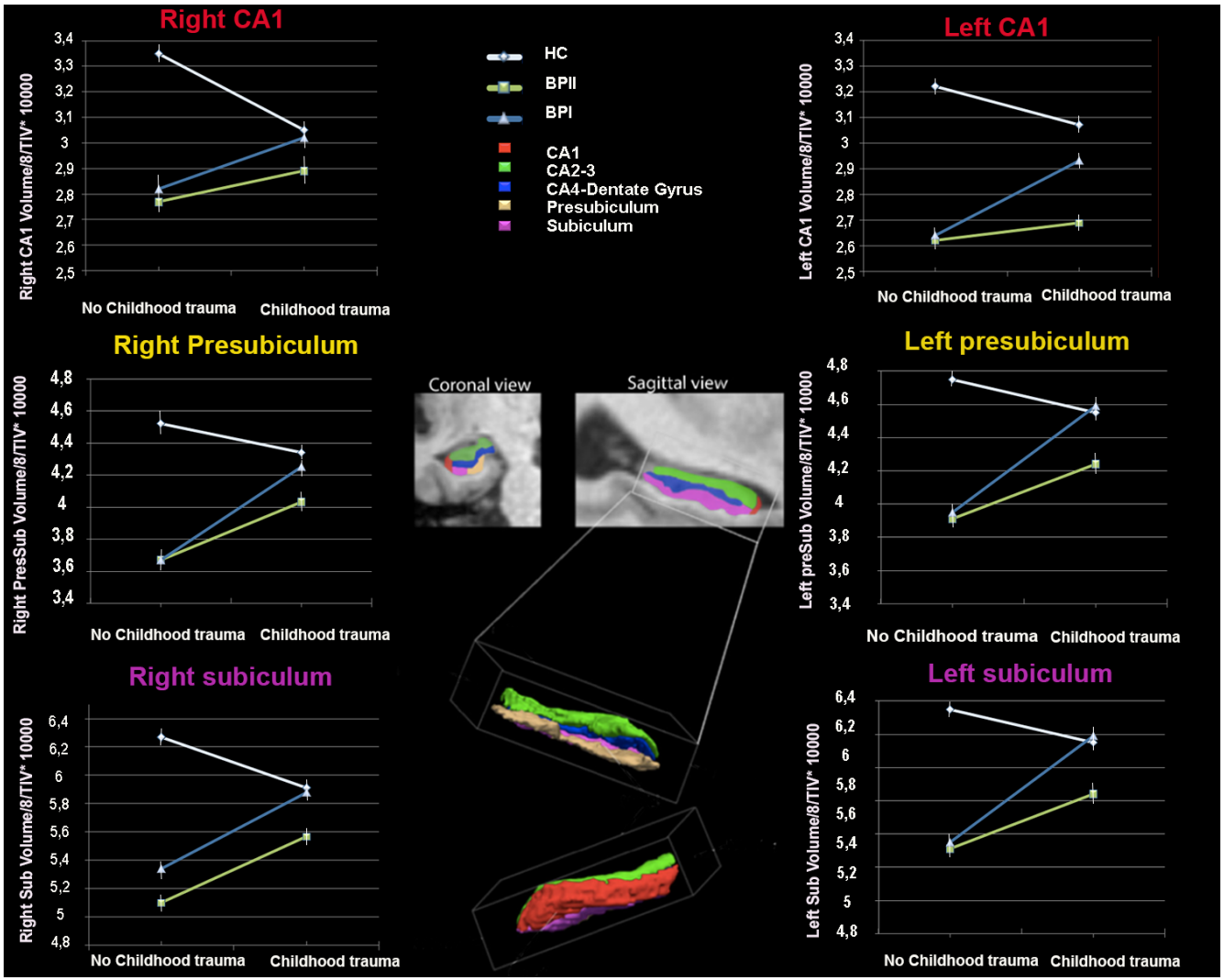

Figure 1 legend:

BDI=patients with Bipolar disorder type I; BDII=patients with Bipolar disorder type II; HC= Healthy comparison individuals; nCT=No childhood trauma; CT=childhood trauma; TIV=total intracranial volume. Means and standard errors of hippocampal subfield volumes are provided.

Table 1 Sociodemographic and clinical characteristics

Characteristics	BDI-CT (n=27)	BDI-nCT (n=29)	BDII-CT (n=25)	BDII-nCT (n=23)	HC-CT (n=20)	HC-nCT (n=61)	F or χ^2	df	*p*
Age (years): mean ± (SD)	43.18 (11.32)	44.90 (13.93)	43.85 (12.43)	44.18 (11.22)	45.80 (12.12)	44.63 (15.67)	0.10	5	0.99
Males: n (%)	10 (37.03)	22 (75.86)	8 (32.00)	12 (52.17)	10 (50.00)	22 (36.06)	16.16	5	0.006*
Educational Level (years): mean ± (SD)	14.18 (4.21)	14.00 (2.94)	13.84 (3.73)	14.73 (2.76)	15.70 (2.77)	14.80 (3.26)	1.00	5	0.41
HAM-D score: mean ± (SD)	8.81 (5.13)	6.17 (5.34)	9.88 (5.46)	8.82 (6.67)	4.10 (2.02)	2.29 (2.14)	17.01	5	<0.0001*
HAM-A score: mean ± (SD)	11.00 (5.77)	5.96 (5.06)	11.68 (6.72)	8.87 (5.46)	6.40 (4.57)	4.13 (3.64)	12.56	5	<0.0001*
YMRS score: mean ± (SD)	7.00 (5.39)	7.06 (8.31)	3.76 (3.28)	4.26 (2.88)	1.65 (1.42)	1.50 (1.43)	10.90	5	<0.0001*
Psychiatric familiarity: n (%)	22 (81.48)	21 (72.41)	18 (72.00)	16 (69.56)	-	-	1.11	3	0.77
Age at onset of illness: mean ± (SD)	27.76 (11.65)	27.89 (11.37)	27.64 (11.73)	29.04 (9.33)	-	-	0.08	3	0.97
Duration of illness (years): mean± (SD)	15.44 (11.52)	17.03 (12.39)	16.48 (10.81)	15.08 (9.76)	-	-	0.16	3	0.91
Drugs:									

Antidepressants *n* (%)	20 (74.07)	17 (58.62)	23 (92.00)	20 (86.95)	-	-	10.10	3	0.01*
Lithium : *n* (%)	18 (66.66)	18 (62.06)	14 (56.00)	9 (39.13)	-	-	4.33	3	0.22
Antipsychotics: *n* (%)	23 (85.18)	26 (89.66)	19 (76.00)	13 (56.52)	-	-	9.31	3	0.02*
Benzodiazepines: *n* (%)	19 (70.37)	22 (75.86)	20 (80.00)	15 (65.21)	-	-	1.54	3	0.67

Legend: BDI-CT= Patients with bipolar disorders type I with childhood trauma; BDI-nCT= Patients with bipolar disorders type I without childhood trauma; BDII-CT=Patients with bipolar disorders type II with childhood trauma; BDII-CT=Patients without bipolar disorders type II with childhood trauma; HC-CT=Healthy controls with childhood trauma; HC-nCT=Healthy controls without childhood trauma; S.D.=Standard deviation; df=Degrees of freedom

Table 2 The effect of childhood trauma and diagnosis on hippocampal subfields (ANOVAs)

	BDI – CT (n=27)	BDI-nCT (n=29)	BDII - CT (n=25)	BDII-nCT (n=23)	HC-CT (n=20)	HC-nCT (*n*=61)	**Childhood trauma**			**Diagnosis**			**Interaction between Childhood trauma and Diagnosis**		
	Mean# ± (SD)	Mean# ± (SD)	Mean# ± (SD)	Mean# ± (SD)	Mean# ± (SD)	Mean# ± (SD)	**F**	**df**	***P***	**F**	**df**	***P***	**F**	**df**	***p***
Right CA1	2.89 0.30	2.77 0.49	3.02 0.46	2.82 0.34	3.05 0.24	3.35 0.33	0.16	1	0.89	15.90	2	**<0.0001**	7.60	2	**0.0007**
Right CA2/3	8.70 1.29	8.37 1.51	9.07 1.40	8.55 1.12	9.65 0.87	10.14 0.95	0.41	1	0.51	21.23	2	**<0.0001**	2.83	2	0.06
Right CA4/DG	4.82 0.65	4.63 0.84	5.09 0.76	4.78 0.60	5.32 0.53	5.63 0.53	0.31	1	0.57	20.76	2	**<0.0001**	3.35	2	0.03
Right Presubiculum	4.03 0.65	3.64 0.63	4.25 0.71	3.67 0.56	4.34 0.66	4.52 0.61	6.97	1	**0.009**	14.00	2	**<0.0001**	5.36	2	**0.005**
Right Subiculum	5.57 0.60	5.10 0.83	5.88 0.86	5.34 0.71	5.91 0.63	6.27 0.59	4.08	1	0.04	17.41	2	**<0.0001**	7.23	2	**0.001**
Left CA1	2.69 0.33	2.62 0.42	2.93 0.48	2.64 0.34	3.07 0.31	3.22 0.31	1.42	1	0.23	28.50	2	**<0.0001**	4.82	2	**0.009**
Left CA2/3	8.15 1.21	7.72 1.39	8.48 1.31	7.92 0.93	9.12 0.92	9.53 0.99	1.15	1	0.28	24.57	2	**<0.0001**	2.99	2	0.05
Left CA4/DG	4.63 0.68	4.33 0.76	4.82 0.76	4.53 0.54	5.09 0.54	5.40 0.53	0.88	1	0.34	22.74	2	**<0.0001**	4.29	2	0.02
Left Presubiculum	4.24 0.76	3.91 0.70	4.59 0.70	3.95 0.59	4.55 0.65	4.75 0.61	5.96	1	**0.01**	11.06	2	**<0.0001**	5.42	2	**0.005**
Left Subiculum	5.56 0.69	5.14 0.85	6.00 0.89	5.35 0.72	6.06 0.63	6.40 0.61	4.70	1	0.03	22.00	2	**<0.0001**	7.11	2	**0.001**

Legend: BDI-CT= Patients with bipolar disorders type I with childhood trauma; BDI-nCT= Patients with bipolar disorders type I without childhood trauma; BDII-CT=Patients with bipolar disorders type II with childhood trauma; BDII-CT=Patients without bipolar disorders

type II with childhood trauma; HC-CT=Healthy controls with childhood trauma; HC-nCT=Healthy controls without childhood trauma; df=Degrees of freedom. #: Volumes are corrected for Total Intracranial Volume (TIV)

Table 3. The effect of diagnosis: t-tests comparisons between groups

	HC vs BDI		HC vs BDII		BDI vs BDII	
	t	*p*	*t*	*p*	*t*	*p*
Right CA1	-7.00	<0.0001	-5.31	<0.0001	-1.12	0.26
Right CA2-3	-7.37	<0.0001	-6.01	<0.0001	-1.09	0.27
Right CA4-DG	-7.45	<0.0001	-5.63	<0.0001	-1.43	0.15
Right Presubiculum	-5.78	<0.0001	-4.18	<0.0001	-1.07	0.28
Right Subiculum	-7.16	<0.0001	-4.33	0.0001	-1.86	0.06
Left CA1	-8.89	<0.0001	-5.86	<0.0001	-1.71	0.09
Left CA2-3	-7.60	<0.0001	-6.28	<0.0001	-1.16	0.24
Left CA4-DG	-7.69	<0.0001	-5.87	<0.0001	-1.44	0.15
Left Presubiculum	-5.32	<0.0001	-3.41	0.0009	-1.48	0.14
Left subiculum	-7.94	<0.0001	-4.68	<0.0001	-2.12	0.03

Legend: BDI= Patients with bipolar disorders type I, BDII= Patients with bipolar disorders type II, HC=Healthy controls

Table 4. The effect of the interaction between diagnosis and childhood trauma: t-tests comparisons between groups.

	Right CA1		Right Presubiculum		Right subiculum		Left CA1		Left presubiculum		Left Subiculum	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
BDI-nCT vs BDI-CT	-1.12	0.26	-2.28	0.02	-2.39	0.02	-0.66	0.50	-1.65	0.10	-2.02	0.04
BDI-nCT vs BDII-nCT	-3.82	0.70	-0.16	0.87	-1.06	0.29	-1.19	0.84	-0.21	0.82	-0.95	0.34
BDI-nCT vs BDII-CT	-1.90	0.06	-3.33	**0.001**	-3.37	**0.001**	-2.49	0.01	-3.51	**0.0009**	-3.62	**0.0007**
BDI-nCT vs nHC-CT	-6.66	**<0.0001**	-6.26	**<0.0001**	-7.55	**<0.0001**	-7.59	**<0.0001**	-5.71	**<0.0001**	-7.99	**<0.0001**
BDI-nCT vs HC-CT	-2.35	0.02	-3.73	**0.0005**	-3.67	**0.0006**	-4.07	**0.0002**	-3.20	**0.002**	-4.11	**0.0002**
BDI-CT vs BDII-nCT	0.84	0.40	2.05	0.04	1.26	0.21	0.49	0.62	1.44	0.15	1.04	0.30
BDI-CT vs BDII-CT	-1.16	0.25	-1.18	0.24	-1.52	0.13	-2.10	0.04	-1.72	0.09	-2.00	0.05
BDI-CT vs HC-nCT	-6.18	**<0.0001**	-3.37	**0.001**	-5.01	**<0.0001**	-7.25	**<0.0001**	-3.30	**0.001**	-5.69	**<0.0001**

BDI-CT vs HC-CT	-1.89	0.06	-1.60	0.11	-1.89	0.06	-4.02	**0.002**	-1.47	0.14	-2.54	0.01
BDII-nCT vs BDII -CT	-1.70	0.09	-3.11	**0.003**	-2.38	0.02	-2.35	0.02	-3.37	**0.001**	-2.75	**0.008**
BDII-nCT vs HC-nCT	-6.56	**<0.0001**	-5.75	**<0.0001**	-6.00	**<0.0001**	-7.38	**<0.0001**	-5.31	**<0.0001**	-6.64	**<0.0001**
BDII-nCT vs HC-CT	-2.51	0.01	-3.58	**0.0009**	-2.78	**0.008**	-4.27	**0.0001**	-3.14	**0.003**	-3.39	**0.001**
BDII-CT vs HC-nCT	-3.79	**0.0003**	-1.73	0.086	-2.36	0.02	-3.33	**0.001**	-1.01	0.31	-2.35	0.02
BDII-CT vs HC-CT	-0.28	0.78	-0.42	0.67	-0.13	0.88	-1.14	0.25	0.19	0.84	-0.24	0.80
HC-nCT vs HC-CT	3.77	**0.0003**	1.10	0.27	2.25	0.02	1.85	0.06	1.21	0.22	2.10	0.04

Legend: BDI-CT= Patients with bipolar disorders type I with childhood trauma; BDI-nCT= Patients with bipolar disorders type I without childhood trauma; BDII-CT=Patients with bipolar disorders type II with childhood trauma; BDII-CT=Patients without bipolar disorders type II with childhood trauma; HC-CT=Healthy controls with childhood trauma; HC-nCT=Healthy controls without childhood trauma