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MRI study of thalamic volumes in bipolar and unipolar patients and healthy individuals

Sheila C. Caetano[a,b], Roberto Sassi[a,b], Paolo Brambilla[a,c], Keith Harenski[a], Mark Nicoletti[a], Alan G. Mallinger[a,d], Ellen Frank[a,e], David J. Kupfer[a,f], Matcheri S. Keshavan[a], Jair C. Soares[a,*]

[a] *Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213-3282, USA*
[b] *Department of Psychiatry, University of Sao Paulo School of Medicine, Sao Paulo, Brazil*
[c] *Department of Psychiatry, University of Pavia School of Medicine, Pavia, Italy*
[d] *Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[e] *Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA*
[f] *Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA*

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Abstract

The thalamus is a key structure in brain anatomic circuits potentially involved in the pathophysiology of mood disorders. Available findings from studies that examined this brain region in mood disorder patients have been conflicting. To examine the hypothesis of anatomical abnormalities in the thalamus in patients with mood disorders, we conducted a magnetic resonance imaging (MRI) study in 25 bipolar patients (mean age ± S.D. = 34.4 ± 9.8 years), 17 unipolar patients (mean age ± S.D. = 42.8 ± 9.2 years), and 39 healthy control subjects (mean age ± S.D. = 36.6 ± 9.7 years). Thalamic volumes Gray Matter were measured blindly with a semi-automated technique. Multivariate analysis of variance, with age and gender as covariates, revealed no significant differences in left or right thalamic volumes among bipolar patients, unipolar patients and healthy individuals. There were no significant effects of gender, age at illness onset, episode type, number of episodes, length of illness, or family history of mood disorders on thalamic measurements. Although functional abnormalities in the thalamus are likely to be implicated in the pathophysiology of mood disorders, no abnormalities in thalamic size appear present in bipolar or unipolar individuals.

Keywords: Thalamus; Bipolar disorder; Unipolar disorder; MRI; Neuroimaging; Brain imaging; Mood disorders

* Corresponding author. Neurochemical Brain Imaging Laboratory, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara St., Pittsburgh, PA 15213, USA. Tel.: +1-412-624-3282; fax: +1-412-624-1496.
E-mail address: soares + @pitt.edu (J.C.).

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1. Introduction

The thalamus has been investigated in brain-imaging studies because it is believed to play a crucial role in the pathophysiology of psychiatric illnesses. This brain region is a key component of the main neuroanatomic circuitries currently hypothesized to be altered in psychiatric illnesses, such as schizophrenia (Andreasen, 1997) and mood disorders (Soares and Mann, 1997). Furthermore, the thalamus is involved in cognitive processes such as attention, which can be impaired not only in schizophrenia (Andreasen, 1997), but also in bipolar (Denicoff et al., 1999; Sax et al., 1999) and unipolar (Mialet et al., 1996) disorders, suggesting that there may be functional or anatomical abnormalities in the thalamus in patients suffering from these illnesses.

Among schizophrenic patients, all controlled MRI studies have reported a reduction (not always statistically significant) in thalamic size (Andreasen et al., 1994; Buchsbaum et al., 1996; Gur et al., 1998; Portas et al., 1998; Staal et al., 1998; Dasari et al., 1999; Hazlett et al., 1999; Ettinger et al., 2001) with one exception (Arciniegas et al., 1999). These findings are also supported by a recent meta-analysis of the available studies (Konick and Friedman, 2001). However, in mood disorder patients, neuroanatomic alterations in the thalamus are still controversial. Hence, Cummings and Mendez (1984), in a case report, found right thalamus infarction to be implicated in secondary mania. A controlled MRI study in first-episode manic patients did not yield significant differences in thalamic volumes in comparison to healthy control subjects (Strakowski et al., 1993). However, in a second study in bipolar patients carried out by these same authors (Strakowski et al., 1999), a medium effect size was reported, with larger thalamus volumes in bipolar patients, whereas another study by a different group of investigators reported a significant enlargement in this brain structure (Dupont et al., 1995). On the other hand, Dasari et al. (1999) found decreased thalamic areas in schizophrenic or bipolar patients compared to healthy control subjects. Furthermore, in functional studies, Drevets et al. (1995) and Buchsbaum et al. (1997) reported alterations of metabolism and blood flow in the medial thalamus in depressed bipolar patients. Deicken et al. (2000) reported higher *N*-acetylaspartate (NAA) levels in the anterior and mediodorsal thalamic regions, suggesting localized neuronal dysfunction. As for unipolar patients, Krishnan et al. (1993) and Buchsbaum et al. (1997) found no abnormalities in thalamic volumes in depressed unipolar patients, in contrast with findings of smaller volumes reported by Dupont et al. (1995). Buchsbaum et al. (1997) also reported decreased glucose metabolism in thalamus in unipolar patients in a PET study. In conclusion, the presence of neuroanatomical abnormalities in thalamus in unipolar and bipolar patients is controversial. Nonetheless, several studies have suggested functional, and possibly neurochemical abnormalities in this brain region in bipolar individuals.

Due to the importance of the thalamus in cognitive and emotional processing, and in view of the conflicting findings from the few available MRI studies that examined this brain region in mood disorder patients, we conducted a controlled MRI study in bipolar and unipolar patients to further investigate possible neuroanatomical abnormalities in thalamus. Based on results of prior studies, we hypothesized that bipolar patients would have increased thalamic size.

2. Materials and methods

2.1. Subjects

Twenty-five bipolar patients (15 males and 10 females, age range from 19 to 56 years old, mean age $\pm$ S.D. = 34.4 $\pm$ 9.8 years) were recruited. Bipolar patients met DSM-IV diagnostic criteria for bipolar type I ($N = 20$) or type II ($N = 5$), and were depressed ($N = 10$), hypomanic ($N = 1$) or euthymic ($N = 14$) at the time of the study. Eleven bipolar patients were lithium-free for a minimum of 1 month (mean age $\pm$ S.D = 38.3 $\pm$ 10.9 years; 6 males, 5 females; 7 bipolar type I, 4 bipolar type II; 7 depressed, 1 hypomanic, 3 euthymic), while

14 patients were on treatment with lithium (mean ± S.D. dose = 1125 ± 389 mg/day, range = 750–2100 mg/day; mean ± S.D. weeks of uninterrupted treatment = 87 ± 119, range = 10–384 weeks; mean ± S.D. age = 31.3 ± 7.9 years; 9 males, 5 females; 13 bipolar type I, 1 bipolar type II; 3 depressed; 11 euthymic). All bipolar patients were free from psychoactive medications (with the exception of lithium in the lithium-treated group) for a minimum of 2 weeks at the point when they participated in the study. Only five patients had a previous history of use of antipsychotic medications.

Seventeen unipolar patients (1 male and 16 females, age range from 24 to 59 years old, mean age ± S.D. = 42.8 ± 9.2 years) were recruited. Unipolar patients met DSM-IV diagnostic criteria for Major Depressive Disorder, and on entering the study, they were depressed ($N = 9$) or euthymic ($N = 8$). All unipolar patients were free of psychotropic medications for a minimum of 2 weeks. Only two of these patients had a previous history of use of antipsychotic medications. All patients were recruited by advertisements in the community, or were referred by the outpatient clinics at the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine. Psychiatric diagnosis was ascertained by the Structured Clinical Interview for DSM-IV (SCID-IV) (Spitzer et al., 1994), and symptom ratings were conducted with the Hamilton Depression Rating Scales (HDRS)-17 and 25 items (Hamilton, 1960). Bipolar patients were also assessed with the Bech–Rafaelsen Mania Scale (BRMS) (Bech et al., 1979). Psychiatric family history, age at onset of illness, length of illness, and number of previous affective episodes were recorded. First-degree relatives were considered positive for mood disorders if they ever received a diagnosis of unipolar or bipolar disorder by a psychiatrist, as ascertained by patient's and relative's reports, and available medical records. Patients did not have any other axis I comorbid psychiatric disorder, current medical problems or alcohol/ substance abuse in the 6 months preceding the study.

Thirty-nine healthy control subjects (25 males and 14 females, age range from 21 to 59 years old, mean age ± S.D. = 36.6 ± 9.7 years old) were recruited, after evaluation with the SCID-IV nonpatient version to rule out psychiatric disorders. They had no current medical illnesses, no past or current psychiatric disorders, no history of alcohol/substance abuse, and no history of having a first-degree relative with a diagnosed psychiatric disorder.

This study protocol was approved by the University of Pittsburgh biomedical IRB, and all subjects signed informed consent after being fully informed about the study.

2.2. Image acquisition

All subjects were scanned at the University of Pittsburgh Medical Center with a 1.5 T GE Signa Imaging System using version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI, USA). Three-dimensional gradient echo imaging (Spoiled Gradient Recalled Acquisition, SPGR) was performed in the coronal plane (TR = 25 ms, TE = 5 ms, nutation angle = 40°, FOV = 24 cm, slice thickness = 1.5 mm, NEX = 1, matrix size = 256 × 192). T2 and proton density images were obtained in the axial plane to screen for neuroradiological abnormalities (Fig. 1).

2.3. Image analysis

Image analysis was carried out with the semi-automated software Scion Image for Windows Beta-3b version (Scion Corporation, Inc., Frederick, MD, USA), on a PC workstation (Dell Dimension, Pentium II 400, Windows NT 4.0). After the identification of the thalamus in the coronal plane, its limits were manually traced. All thalamic measurements were carried out by a well-trained rater, who achieved an intra-class correlation coefficient, $r > 0.93$ for the right, and $r > 0.94$ for the left thalamus. Thalami were measured blindly to subject's identity or group assignment.

The thalamic gray matter volumes (cm^3) were obtained by multiplying the measured areas (cm^2) by the slice thickness (0.15 cm). The resulting thalamus volumes were corrected for differences

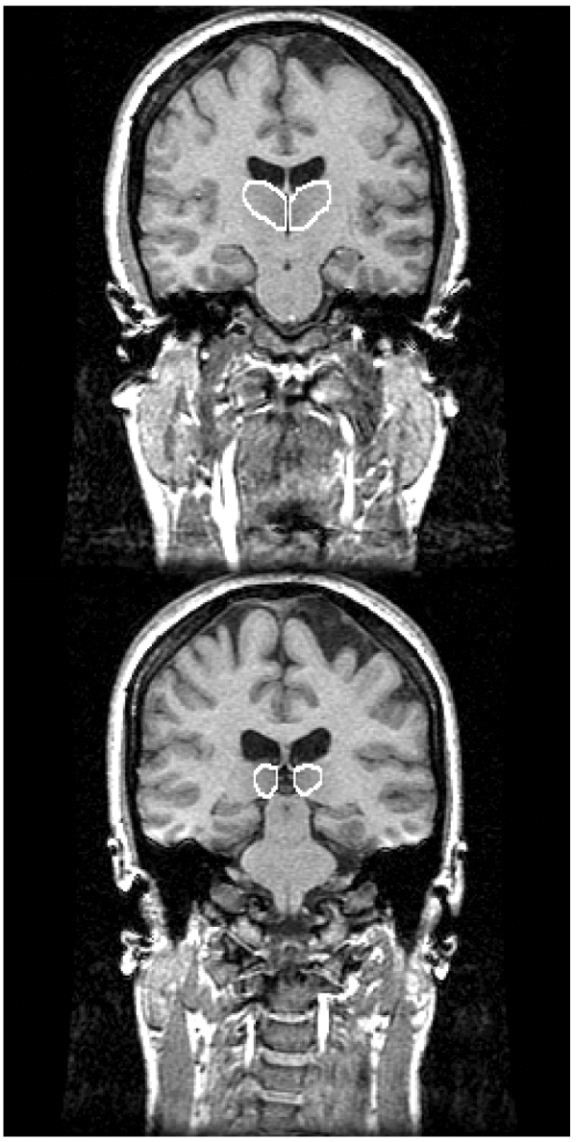

Fig. 1. An illustration of the tracing of the thalamus on an SPGR MRI, at two different slices in the coronal plane.

in brain size by dividing individual values by the intra-cranial volume (ICV) measurements, and multiplying the result by the mean ICV for the whole sample.

The ICV measurements were obtained by manually tracing in the coronal plane, by a well-trained rater (M.N.), and were calculated by multiplying the total area by 0.3 cm, as every other slice was considered for these measurements. The ICC for the ICV measures was 0.97.

2.4. Neuroanatomical landmarks

The thalamus tracing began at the coronal slice where the pons first appeared, and continued until the slice where it was no longer possible to distinguish the thalamus from the surrounding brain matter. The lateral ventricles at the superior border, the substantia nigra at the inferior border, the internal capsule at the lateral border, and the third ventricle at the medial border demarcated the limits of the thalamus. By the middle slice, the inferior border was already the superior colliculus.

2.5. Intra-cranial brain volume

For the intra-cranial brain volumes (ICVs), brain matter was traced along the outside border of the brain. Total cerebral gray and white matter (including brainstem, temporal lobes, the optic chiasma, the pituitary and cerebellum), CSF, dura matter, and synuses were included. All odd slices were considered. The base of the cerebellum demarcated the inferior border.

2.6. Statistical analyses

Statistical analyses were performed with SPSS for Windows software, version 10.0 (SPSS Inc., Chicago). Anatomical comparisons among bipolar patients, unipolar patients and healthy control subjects were carried out by means of multivariate analysis of variance (MANOVA), with age and gender as covariates, and utilizing a P value of 0.05. Pearson's correlation coefficients were calculated to assess the relationship between age and thalamic volumes. The correlation between thalamic volumes and those clinical variables that did not display a normal distribution (length of illness, number of previous affective episodes, age of illness onset, and total scores on Hamilton 17- and 25-item scales) was examined with Spearman's correlation coefficients. The potential effects of

mood state and family history of mood disorders on thalamic measurements were analyzed by MANOVA, with age and gender as covariates.

3. Results

The thalamic gray matter volumes, after correction for individual ICVs, are represented in Table 1. Bipolar patients, unipolar patients, and healthy control subjects did not differ significantly in measures of left, right, or total (combined) thalamic volumes (MANOVA, age and gender as covariates, $P > 0.05$ — see Table 1).

Age was not significantly correlated with thalamic volumes in bipolar or unipolar patients or healthy control subjects (Pearson correlation coefficients, $P > 0.05$: left: $r = -0.74$, $P = 0.51$; right: $r = 0.05$, $P = 0.66$; and total thalamic volume: $r = -0.01$, $P = 0.93$). Female ($n = 40$) compared with male subjects ($n = 41$) had no significant differences in left (mean ± S.D. = 3.59 ± 1.08 ml and 3.35 ± 0.90 ml, respectively; MANOVA, age as covariate: $F = 1.68$, d.f. = 1.78, $P = 0.20$), right (mean ± S.D. = 3.59 ± 1.07 ml and 3.46 ± 1.09 ml; MANOVA, age as covariate: $F = 0.22$, d.f. = 1.78, $P = 0.64$), and total thalamus volumes (mean ± S.D. = 7.18 ± 2.11 ml and 6.81 ± 1.74 ml; MANOVA, age as covariate: $F = 0.86$, d.f. = 1.78, $P = 0.36$).

No statistically significant correlation was found between any anatomical measurements and length of illness (bipolar patients: left: rho = −0.36, $P = 0.08$; right: rho = −0.09, $P = 0.68$; and total thalamus volumes: rho = −0.21, $P = 0.31$; and unipolar patients: left: rho = −0.13, $P = 0.63$; right: rho = −0.14, $P = 0.58$; and total thalamus volumes: rho = −0.15, $P = 0.55$), number of prior affective episodes (bipolar patients: left: rho = −0.08, $P = 0.72$; right: rho = 0.01, $P = 0.97$; and total thalamus volumes: rho = 0.44, $P = 0.84$; and unipolar patients: left: rho = 0.17, $P = 0.52$; right: rho = 0.26, $P = 0.92$; and total thalamus volumes: rho = 0.92, $P = 0.72$), age at illness onset (bipolar patients: left: rho = −0.27, $P = 0.19$; right: rho = −0.23, $P = 0.27$; and total thalamus volumes: rho = −0.30, $P = 0.15$; and unipolar patients: left: rho = −0.05, $P = 0.85$; right: rho = −0.01, $P = 0.97$; and total thalamus volumes: rho = −0.03, $P = 0.90$), or HDRS scores (Hamilton 25-items) (bipolar patients: left: rho = −0.25, $P = 0.30$; right: rho = −0.28, $P = 0.25$; and total thalamus volumes: rho = −0.22, $P = 0.35$; and unipolar patients: left: rho = 0.12, $P = 0.65$; right: rho = 0.24, $P = 0.39$; and total thalamus volumes: rho = 0.20, $P = 0.48$) (Spearman correlation coefficients, $P > 0.05$).

Additionally, there were no significant differences in thalamic measurements among the following patient subgroups: (1) depressed bipolar ($n = 10$) and euthymic bipolar ($n = 14$) patients (MANOVA, age and gender as covariates, $P > 0.05$: left: $F = 0.58$, d.f. = 1.20, $P = 0.46$, right: $F = 1.04$, d.f. = 1.20, $P = 0.32$, and total thalamic volumes: $F = 0.88$, d.f. = 1.20, $P = 0.36$); (2) depressed unipolar ($n = 9$) and euthymic unipolar ($n = 8$) patients (MANOVA, age and gender as covariates, $P > 0.05$: left: $F = 0.02$, d.f. = 1.13, P

Table 1
Measures of thalamic Gray Matter volumes

Volumes (ml)	BP patients ($N = 25$) (mean ± S.D.)	UP patients ($N = 17$) (mean ± S.D.)	Normal control subjects ($N = 39$) (mean ± S.D.)	Statistics MANOVA (F, d.f., P)
Left thalamus	3.52 ± 1.23	3.60 ± 0.89	3.37 ± 0.88	0.17, 2, 76, 0.85
Right thalamus	3.51 ± 1.29	3.65 ± 0.88	3.48 ± 1.02	0.05, 2, 76, 0.95
Total (combined) thalamus	7.03 ± 2.42	7.26 ± 1.73	6.84 ± 1.68	0.11, 2, 76, 0.90

All values presented were ICV-corrected. MANOVA was conducted with age and gender as covariates. BP, bipolar, UP, unipolar.

= 0.90, right: $F = 0.03$, d.f. = 1.13, $P = 0.85$, and total thalamic volumes: $F = 0.001$, d.f. = 1.13, $P = 0.98$); (3) euthymic bipolar and euthymic unipolar patients (MANOVA, age and gender as covariates, $P > 0.05$: left: $F = 0.57$, d.f. = 1.18, $P = 0.46$, right: $F = 0.39$, d.f. = 1.18, $P = 0.54$, and total thalamic volumes: $F = 0.50$, d.f. = 1.18, $P = 0.49$); (4) depressed bipolar and depressed unipolar patients (MANOVA, age and gender as covariates, $P > 0.05$: left: $F = 0.00$, d.f. = 1.15, $P = 0.98$, right: $F = 0.17$, d.f. = 1.15, $P = 0.69$, and total thalamic volumes: $F = 0.05$, d.f. = 1.15, $P = 0.83$).

Furthermore, no significant differences were found between lithium-treated bipolar patients ($N = 14$) and drug-free bipolar patients ($n = 11$) for left (mean ± S.D. = 3.63 ± 1.18 ml and 3.38 ± 1.34 ml, respectively; MANOVA, age and gender as covariates: $F = 0.22$, d.f. = 1.21, $P = 0.88$), right (mean ± S.D. = 3.47 ± 1.33 ml and 3.57 ± 1.30 ml, respectively; MANOVA, age gender as covariates: $F = 0.43$, d.f. = 1.21, $P = 0.52$), or total thalamus volumes (mean ± S.D. = 7.10 ± 2.39 ml and 6.95 ± 2.56 ml, respectively; MANOVA, age and gender as covariates: $F = 0.19$, d.f. = 1.21, $P = 0.67$).

No statistically significant differences were found for any thalamic measurements between familial ($n = 12$) and non-familial bipolar patients ($n = 13$) (left: mean ± S.D. = 3.59 ± 1.45 ml and 3.45 ± 1.04 ml, respectively; MANOVA, age and gender as covariates: $F = 0.15$, d.f. = 1.21, $P = 0.70$; right: mean ± S.D. = 3.46 ± 1.62 ml and 3.56 ± 0.96 ml, respectively; $F = 0.04$, d.f. = 1.21, $P = 0.83$; and total thalamus volumes: mean ± S.D. = 7.06 ± 2.97 ml and 7.01 ± 1.89 ml, respectively; $F = 0.01$, d.f. = 1.21, $P = 0.94$). No significant differences were found between familial ($n = 7$) and non-familial unipolar patients ($n = 5$) (left: mean ± S.D. = 3.42 ± 0.76 ml and 3.90 ± 0.99 ml, respectively; MANOVA, age and gender as covariates: $F = 1.37$, d.f. = 1.8, $P = 0.28$; right: mean ± S.D. = 3.39 ± 0.79 ml and 4.01 ± 1.06 ml, respectively; $F = 1.13$, d.f. = 1.8, $P = 0.32$; and total thalamus volumes: mean ± S.D. = 6.81 ± 1.53 ml and 7.91 ± 1.97 ml, respectively; $F = 1.29$, d.f. = 1.8, $P = 0.29$).

4. Discussion

We found no abnormalities in measures of right, left, and total thalamus volumes in bipolar and unipolar patients. The findings for the bipolar patients are not in agreement with prior reports of enlarged (Dupont et al., 1995; Strakowski et al., 1999) or reduced thalamic size (Dasari et al., 1999); but are in line with a negative report involving first-episode manic patients (Strakowski et al., 1993), and another study involving a small sample ($n = 9$) of bipolar patients (Buchsbaum et al., 1997). In unipolar patients, our negative findings are consistent with most prior reports (Krishnan et al., 1993; Buchsbaum et al., 1997), with the exception of the report of Dupont et al. (1995), suggesting smaller thalamic volumes. In conclusion, our results are in agreement with most of the prior literature findings in this area, and suggest that no identifiable abnormalities in thalamic size are present in mood disorder patients.

In our subject sample, there were no significant gender effects on thalamic volumetric measurements. These findings are in agreement with Konick and Friedman (2001) and Arciniegas et al. (1999), who did not report any gender differences in thalamic size in schizophrenic patients or healthy individuals, but are in conflict with the report by Parashos et al. (1998), who found larger thalamic volumes in females compared to males.

Furthermore, no significant effects of length of illness, age at illness onset, number of prior affective episodes, and depression severity (HDRS scores) were found on any of the thalamic measurements. Strakowski et al. (1999) also reported no significant relationship between thalamic measures and clinical variables (length of illness and number of prior affective episodes) in bipolar patients. Moreover, no evidence of significant effects of mood state or family history of mood disorders on thalamic measures was found in bipolar or unipolar patients. Last, no significant differences in thalamic volumes were found between drug-free ($n = 11$) and lithium-treated bipolar patients ($n = 14$). However, the small number of patients involved in this particular comparison is a potential limitation, and possible

effects of long-term lithium treatment in these brain structures cannot be fully ruled out based solely on our present findings.

In conclusion, we were unable to identify abnormalities in thalamic size in bipolar or unipolar patients. These findings are in agreement with most of the prior reports in this area, suggesting that this may be an important distinction when one compares the neuropathology of bipolar and unipolar mood disorders to the neuropathology of schizophrenia, where findings of smaller size of the thalamus have been replicated in several studies. Moreover, age, gender, length of illness, age at illness onset, number of prior affective episodes, mood state, and family history of mood disorders do not seem to significantly affect thalamic size in bipolar and unipolar patients. Nonetheless, as our subject samples were primarily composed of outpatients, with relatively mild illness severity and illness course, these findings should be further investigated in studies involving larger and more severe patient samples, in order to longitudinally assess the possible relevance of anatomical or functional thalamic abnormalities in the mechanisms potentially involved in mood disorders.

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