Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 1245–1249

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Increased pituitary volume in patients with established bipolar affective disorder

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ARTICLE INFO

Article history:
Received 23 June 2009
Received in revised form 13 July 2009
Accepted 13 July 2009
Available online 19 July 2009

Keywords:
Bipolar disorder
Hypothalamic-pituitary-adrenal axis
Magnetic resonance imaging
Pituitary gland

ABSTRACT

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been demonstrated in bipolar disorder (BD), but previous magnetic resonance imaging (MRI) studies of pituitary gland volume in BD have reported variable findings. In this MRI study we investigated pituitary volume in 26 patients with established bipolar I disorder (8 males and 18 females, mean age = 38.4 years) and 24 matched controls (7 males and 17 females, mean age = 38.7 years). The BD patients had a significantly larger pituitary volume as compared with controls, but there was no association between pituitary volume and illness duration, number of manic/depressive episodes, daily medication dosage, family history, or clinical subtype (i.e., psychotic and nonpsychotic). Pituitary volume was larger in females than in males for both groups. These results support previous neuroendocrine findings that implicate HPA axis dysfunction in the core pathophysiological process of BD.

1. Introduction

Abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis, the primary biological system mediating the stress response, are thought to reflect stress-related dysregulation and have been described in patients with mental illnesses ranging from chronic fatigue syndrome to dementia (Cleare et al., 1999), but are particularly pronounced in those affected by mood disorders including bipolar disorder (BD) (reviewed by Daban et al., 2005). Neuroendocrine findings of HPA axis hyperactivity in both remitted and non-remitted BD patients (Schmider et al., 1995; Watson et al., 2004) further suggest its role for the core pathophysiological process in BD.

To date, only a few MRI studies of BD have examined the volume of the pituitary gland, a potential marker of functional status of HPA axis (Axelson et al., 1992), and the results have been controversial. Studies early in the course of BD demonstrated increased (MacMaster et al., 2008) or unchanged (Chen et al., 2004) pituitary volume, while one study reported decreased volume in chronic BD patients (Sassi et al., 2001). Mondelli et al. (2008) examined a sample of established psychotic BD with genetic susceptibility but found no pituitary changes. These inconsistencies between reports might be partly explained by pituitary volume reduction with age (Lurie et al., 1990; Takano et al., 1999) or as a consequence of chronic HPA dysfunction later in the illness course (Chen et al., 2004; Daban et al., 2005), but length of illness was not related to pituitary volume in these studies (Chen et al., 2004; Mondelli et al., 2008; Sassi et al., 2001). Illness heterogeneity (e.g., bipolar I or II, psychotic or nonpsychotic), family history of psychiatric diseases, and treatment status such as medication with mood stabilizers could also affect HPA axis function (Daban et al., 2005), but the potential effects of these clinical factors on pituitary volume in BD remain unclear and further data are needed to evaluate the role of HPA axis dysregulation in the neurobiology of BD.

In the present study, we used MRI to investigate pituitary volume in a relatively homogeneous cohort of established bipolar I disorder and age- and gender-matched healthy comparison participants. On the basis of the HPA hyperactivity model of BD (Daban et al., 2005), we predicted that the BD patients would have larger pituitary volume compared to healthy controls. We also examined whether pituitary volume was related to medication, clinical subgroups (e.g., psychotic or nonpsychotic, family history), or other features of illness.

Abbreviations: ACTH, adrenocorticotropic hormone; ANCOVA, analysis of covariance; BD, bipolar disorder; CSF, cerebrospinal fluid; HPA axis, hypothalamic-pituitary-adrenal axis; ICV, intracranial volume; MRI, magnetic resonance imaging; NART, National Adult Reading Test; SCID-IV-P, Structured Clinical Interview for DSM-IV patient version; SCID-NP, Structured Clinical Interview for DSM-IV nonpatient version.

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doi:10.1016/j.pnpbp.2009.07.012

2. Methods

2.1. Participants

Twenty-six patients with DSM-IV bipolar I disorder (8 males and 18 females; mean age = 38.4 years, SD = 10.9) and 24 age- and gender-matched healthy controls (7 males and 17 females; mean age = 38.7 years, SD = 11.1) participated in this study (Table 1). Patients were recruited through advertisement and via a dedicated specialist bipolar disorder clinic based in Sydney, Australia. Diagnoses were made by a research psychiatrist (GM) using the Structured Clinical Interview for DSM-IV (SCID-IV-P) (First et al., 1998), supplemented by case note review. The majority of patients were euthymic at the time of scanning but experienced subsyndromal symptoms. Controls were recruited predominantly via advertisement and were screened for a personal and family history of psychiatric or neurological disorder using the SCID-IV nonpatient version (SCID-NP). Participants were right-handed and excluded if they had a history of ongoing substance misuse, neurological disease or, in patients, if there was a co-morbid Axis I or II DSM-IV diagnosis that required treatment. All participants gave written informed consent prior to participating and the local Hospital and University ethics committee approved the study.

At the time of scanning, eight patients were taking lithium, seven were taking valproate, and four were taking a combination of both. One patient was taking valproate and carbamazepine and another was taking carbamazepine alone, while five patients were medication free. All patients had previously been exposed to antipsychotic medication, although none within 12 months of entering the study. Ten patients had a family history of major affective disorders (bipolar disorder, $N=3$; unipolar depression, $N=5$; and both, $N=2$), while twelve had no family history of affective disorders and four had an unknown family history. Sixteen patients had a history of psychosis (i.e., hallucinations and/or delusions) during at least one affective episode.

2.2. Magnetic resonance imaging procedures

MR scans were acquired with a 1.5-T GE Signa scanner. A structural T1-weighted image was acquired, with time to echo = 5.3 ms, time repetition = 12.2 ms, field of view = 24.9 cm, and voxel dimensions = 0.98 × 0.98 × 1.6 mm thick coronal slices. The intracranial volume (ICV) was measured on T1-weighted images to correct for differences in head size as previously described (Eritaia et al., 2000); the groups did not significantly differ in their ICVs (Table 1).

The image data were processed using the software package Dr View 5.3 (AJS, Tokyo, Japan). Brain images were realigned in three dimensions to adjust for differences in head tilt during image acquisition and were then reconstructed into entire contiguous coronal images, with a 0.98-mm thickness, perpendicular to the anterior commissure–posterior commissure line. The signal-intensity histogram distributions from the T1-weighted images across the whole cerebrum were then used to automatically segment the voxels into brain tissue compartments and cerebrospinal fluid.

2.3. Pituitary measurements

The volume of the pituitary gland was manually traced on consecutive 0.98-mm coronal slices based on a method used by Garner et al. (2005). Briefly, we traced around the usually well-defined borders of anterior and posterior pituitary: the diaphragma sellae, superiorly; the sphenoid sinus, inferiorly; and the cavernous sinuses, bilaterally. As presented in Fig. 1, the pituitary stalk was excluded from the tracings, but we included a posterior bright spot, corresponding to the posterior pituitary (the intensity of which is thought to reflect vasopressin concentrations).

All measurements reported here were carried out by one rater (TT) without knowledge of the subjects' identities. Inter- (TT and VL) and intra-rater intraclass correlation coefficients in a subset of 10 randomly selected brains were both over 0.93.

2.4. Statistical analysis

Statistical difference in the absolute pituitary volume was analyzed using analysis of covariance (ANCOVA) with age and ICV as covariates, with diagnosis and gender as between-subject factors. The pituitary volume of the patient subgroups (psychotic and nonpsychotic, with and without a family history, with and without lithium or valproate treatment at scanning) was also analyzed by ANCOVA, covarying for age and ICV. Post hoc Scheffé's tests were carried out to follow up any significant main effects or interactions.

Pearson's correlation coefficients were calculated to examine relationships between relative pituitary volume [(absolute volume/

Table 1
Sample characteristics and brain measures.

Variable	Healthy controls		Bipolar patients		Group comparisons	
	Male	Female	Male	Female	Diagnosis effect	Gender effect
	($N=7$)	($N=17$)	($N=8$)	($N=18$)		
Age (years)	41.0 ± 10.3	37.7 ± 11.5	40.5 ± 9.8	37.4 ± 11.4	$F(1, 46)=0.01$, $P=0.91$	$F(1, 46)=0.86$, $P=0.36$
NART-estimated IQ[a]	109.3 ± 10.4	117.5 ± 8.4	112.9 ± 8.6	114.2 ± 6.7	$F(1, 45)<0.01$, $P=0.96$	$F(1, 45)=3.38$, $P=0.07$
Education (years)	14.1 ± 2.4	14.8 ± 2.0	13.5 ± 2.8	15.2 ± 2.7	$F(1, 46)=0.02$, $P=0.89$	$F(1, 46)=2.34$, $P=0.13$
Illness duration (years)	–	–	10.0 ± 12.9	15.1 ± 8.6	–	$F(1, 24)=1.40$, $P=0.25$
No. manic episodes	–	–	5.6 ± 6.6	10.3 ± 11.3	–	$F(1, 24)=1.17$, $P=0.29$
No. depressive episodes	–	–	7.8 ± 8.0	12.6 ± 11.7	–	$F(1, 24)=1.13$, $P=0.30$
Lithium dose (mg/day) ($N=12$)	–	–	917 ± 144 ($N=3$)	994 ± 236 ($N=9$)	–	$F(1, 10)=0.28$, $P=0.61$
Valproate dose (mg/day) ($N=12$)	–	–	1500 ± 500 ($N=3$)	1416 ± 648 ($N=9$)	–	$F(1, 10)=0.04$, $P=0.84$
ICV (cm^3)	1604 ± 163[b]	1403 ± 95	1555 ± 144[b]	1441 ± 102	$F(1, 45)=0.03$, $P=0.86$	$F(1, 45)=21.20$, $P<0.01$
Pituitary gland (mm^3)	614 ± 82	724 ± 117[c]	722 ± 280[d]	849 ± 194[c,d]	$F(1, 44)=5.72$, $P=0.02$	$F(1, 44)=12.04$, $P<0.01$

Data are presented as mean ± SD. ICV, Intracranial volume; NART, National Adult Reading Test.
ANOVA or ANCOVA (brain measures) followed by Scheffé's test was used. Age was used as a covariate for the ICV.
[a] Data missing for one male bipolar patient.
[b] $P<0.01$: compared to females.
[c] $P<0.05$: compared to males.
[d] $P<0.05$: compared to controls.